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13. ABSTRACT ***(Maximum 200 Words)***

This report marks the completion of the first year of the project "Natural History of Plexiform Neurofibromas in NF1." The goals of the project are to test the utility of volumetric MRI in the measurement of plexiform neurofibromas, to use this approach to develop a body of normative data on the growth of plexiform neurofibromas, and to establish an infrastructure including radiology, statistical analysis, clinical database, tissue bank, and pathology review that will facilitate future clinical trials. This first year was devoted to developing the infrastructure of the project and initiating subject recruitment. Major accomplishments include holding a conference at the Banbury Center at which the protocol was refined, establishing MRI data transfer between the participating centers and the radiology analysis facility at WorldCare, creation of the clinical data entry forms, and establishing the communications between the participating centers and the coordinating center in Boston. Patient recruitment has begun, but has been delayed because of a longer than anticipated time required for the approval by the army IRB of the local informed consents. This process is nearing completion, and it is anticipated that subject recruitment will be complete within an additional six months.

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PI - Signature 10/29/99 Date

Table of Contents

Attachments

Introduction

This report marks the completion of the first year of the project "Natural History of Plexiform Neurofibromas in NF1." Plexiform neurofibromas are benign nerve sheath tumors that involve multiple nerve fascicles. They can lead to major disfigurement and morbidity. Treatment is currently limited to surgery, but complete resection is rarely possible. This project is intended to set the stage for clinical trials by developing a reliable approach to measuring tumor volume, as well as a body of normative data on growth rate of the tumors. It is also intended to assemble a consortium of clinical centers united by facilities in radiology, statistics, pathology, clinical data collection, and tissue banking.

The first year of the study was aimed at developing the infrastructure of the project and recruiting study subjects. The complexity of the project made it necessary to bring together all of the participants for a very productive three day meeting at the Banbury Center at Cold Spring Harbor, N.Y. in February. This made it possible to refine the entry and exclusion criteria, study protocol, and methods of communication and data tracking.

Although centers were technically prepared to recruit subjects by May, 1999, we encountered serious problems with Army IRB approval of each center's consent forms. In many cases this has required multiple iterations of revisions both by the Army and local IRB's, both creating frustration and delaying subject recruitment. Most of this process is now completed, and subject recruitment has begun. We expect recruitment to continue through the spring of 2000, likely necessitating extension of the study, which will be possible given that delays in recruitment reduced expenditures this year.

The following report will focus on our progress in setting up the study infrastructure and will exemplify some of the radiological data received to date.

Progress Report for Statement of Work by Task

Task 1. Complete development of study infrastructure – Months 1-6

a. IRB approval at all clinical sites

All of the clinical sites have obtained IRB approval from their own institutions. As of October 1, 1999 only 4 clinical centers have obtained IRB approval from the US Army. This is mainly due to the unanticipated lengthy turn-around time for Army IRB approval, and staff turnover at the MCMR last winter. Copies of the Children's Hospital consent forms, which have been approved by both Children's Hospital IRB and the Army IRB, are located in Appendix B of Attachment A. A complete listing of

the status of Army IRB approval of participating clinical centers provided by the Army is located in Attachment B.

A complete list of all participating centers is located Appendix A of the Policy and Procedure Manual (Attachment A). We have also added two centers to the consortium since the approval of this grant. The following Principal Investigators and their centers have been added:

Jan Friedman, M.D., Ph.D.
University of British Columbia
British Columbia Children's Hospital
Vancouver, BC CANADA

Fernando Kok, M.D.
Universidad de Sao Paulo
San Paulo, BRAZIL

In the original application we stated that John Mulvihill, M.D., Ph.D. would be the Principal Investigator at the University of Pittsburgh. Dr. Mulvihill has since taken a new position at the University of Oklahoma, Children's Hospital of Oklahoma. Dr. Mulvihill is continuing his role in the consortium at the University of Oklahoma.

b. **Complete clinical data entry forms and test electronic transfer of clinical data**

We elected not to use electronic clinical data entry forms to collect the data. This decision was based on concerns about confidentiality of data and the development of scannable forms by The International Neurofibromatosis Database at the University of British Columbia. This simplified data entry, avoided concerns about transmittal of clinical data over the internet, and permitted the participating centers to maintain a paper copy of clinical data that is necessary for a clinical trial. A data entry form specific to this study of plexiform neurofibromas was created. We are also using the standard demographic data collection form as well as the core NF data collection form. By using these forms, patients from this study will be entered into the database in the same format as patients from centers that regularly participate in the International Neurofibromatosis Database. Data collection forms and instructions for their use are located in Appendices G-H of the Policy and Procedure Manual (Attachment A).

c. **Organize package of materials for pathology review and tissue repository**

Please see Section I of the Policy and Procedure Manual located (Attachment A). In this manual we have included instructions for collection of blood and serum.

David Gutmann, M.D., Ph.D. has submitted a progress report for the Neurofibroma Tumor Repository. Please see Attachment C.

It has been necessary to change the structure of the pathology review core. This was originally a subcontract to Dr. David Wolfe at Mt. Sinai School of Medicine. We have found it to be awkward, however, to split the responsibility of tissue collection between two sites, namely the tissue bank and the pathology review site. Moreover, other commitments by Dr. Wolfe have made it difficult for him to provide the level of attention to this project that it requires. We therefore propose that the pathology review facility be moved to Washington University School of Medicine in St. Louis, the site of the tissue bank. Dr. Arie Perry, a neuropathologist at Washington University, has agreed to take responsibility for this role. His CV and a letter of agreement are presented in Attachment D. No funds have been expended for neuropathology review to date, given the problems in the Mt. Sinai facility and the fact that delays in IRB approval have delayed the accession of study subjects. As subject recruitment is now accelerating, this is a good time to make the change to consolidate all tissue collection functions of the project into a single facility.

d. **Set up listserve and website**

The website has been constructed, and will be available to the public by the end of November. A printout of the website is located in Attachment E.

We are in the process of creating a listserve. Communications between participating centers have been accomplished by e-mail and fax, reducing the urgency of a listserve for communication.

e. **Test MRI data transfer**

WorldCare, Inc. has submitted a progress report, which is presented in Attachment F.

f. **Purchase workstation and prepare data entry forms at WorldCare.**

The workstation was purchased in November of 1998. Please see the invoice and description of the equipment in Attachment G.

Data collection forms have been created to track MRI data, which is sent over the Internet using the FTP method, or saved to an optical disk and shipped. There is a data collection form, which must be completed to document the MRI, and three acquisition protocols. The acquisition protocol used depends on the location of the plexiform neurofibroma. Copies of these forms are located in Appendices L-N of the Policy and Procedure Manual (Attachment A).

When a file is transferred or shipped, the clinical center faxes the data collection form and the acquisition protocol to Mary Sanford, the research study coordinator, at Children's Hospital. This alerts the study coordinator that an MRI has occurred and the step is checked off on the project monitoring flowsheet. Once WorldCare has received the data, and confirmed that it is readable, a Confirmation Fax is sent to both Children's Hospital and the center from which it originated. A flowchart of the process in located in Appendix O of the Policy and Procedure Manual (Attachment A).

g. **Prepare project monitoring flowsheet at Children's Hospital**

At this time we are using an Excel spreadsheet to track progress. The workbook is designed to track the data for the entire duration on the study, which will include 7 visits per study subject. This report only includes patient visit #1 of the study-tracking workbook (Attachment H), because no patients have been seen more than once. There are 6 worksheets (Groups A-F) for the 3 plexiform categories and for both children and adults.

h. **Prepare recruitment letters for study subjects**

We decided to hold an open house rather than sending out a patient recruitment letter. In addition to the open house, Gretchen Schneider, M.S., reviewed medical records of NF patients with plexiform neurofibromas and personally contacted them about possible enrollment in the study.

i. **Publicize study to NF community**

Children's Hospital held an open house to inform the public of the progress of NF research and to publicize the study on July 16, 1999. Bruce Korf, and Gretchen Schneider presented an overview of the study for NF patients and families, as well as information on upcoming clinical trials. A copy of the announcement, which was mailed to over 500 NF patients, is located in Attachment I.

Task 2. ***Recruitment of Study Subjects*** **– Months 6-12**

a. **Centers contact prospective study subjects**
b. **Enrollment of study subjects**
c. **First MRI and clinical data received**

Tasks a-c have been delayed due to the problems with the IRB approval process. Once centers receive Army IRB approval they immediately begin enrollment. All centers have been actively promoting and recruiting patients.

Please see the Study-Tracking Sheet (Attachment H) for enrollment and clinical data received.

Please see the progress report provided by WorldCare for information on MRI data received (Attachment F).

d. **Review of clinical entry criteria**

A three-day meeting devoted to this study was held in February 1999 at the Banbury Center in Cold Spring Harbor, N.Y. This meeting was jointly sponsored by the U.S. Army through this project and by the National Neurofibromatosis Foundation. A complete list of participants and the meeting agenda are provided in Attachment J. All of the core facilities of the project and all of the participating centers except one (Australia) were

represented at the meeting. The meeting was intended to review the protocol and make amendments prior to the initiation of subject recruitment. Following the meeting, a detailed protocol manual (Attachment A) was created and provided to all the participating centers. Details of these changes are located in Section D of Attachment A. Changes were made from the original protocol as follows:

1. The three study groups were modified. Originally these were cranial nerve, spinal nerve, and peripheral nerve. It was decided that there might be ambiguity in determining the nerve of origin of some tumors, and that a more clinically based classification scheme would be easier to use in a consistent manner. Therefore, the three study groups were changed to head/neck, trunk/extremity externally visible, and trunk/extremity not externally visible. The definition of plexiform neurofibroma also was clarified, to confine the study to tumors with a potential to cause disfigurement or functional disability.

2. Exclusion criteria were clarified to include previous radiation therapy, current antineoplastic therapy, surgery within six months of the onset of the study (excluding biopsy), and failure to obtain an MRI within 60 days of enrollment.

3. Changes were made in the MRI acquisition protocol to insure complete coverage of the neurofibroma and minimize scanning time.

e. **Test of inter-observer reproducibility of designation of tumor margins by MRI**

Due to the delayed patient recruitment we have been unable to complete the Reproducibility Study as planned. A meeting of the steering committee occurred on September 10, 1999 to design the Reproducibility Study. The radiologists working on the study from Children's Hospital are meeting at WorldCare November 2, 1999 to review the first sets of data. A final report is expected by the end of November.

Task 3. ***Data Acquisition and analysis*** **– Months 13-42**

Not Applicable at this time

Task 4. ***Interpretation of Data*** **– Months 43-48**

Not Applicable at this time

KEY RESEARCH ACCOMPLISHMENTS

- International meeting at Banbury Center of all study participants to refine and finalize the protocol in February 1999
- Completion of procedures and policies manual
- Set up of MRI data analysis center at WorldCare and successful transfer of test data from participating clinical centers
- Establishment of communication system between clinical centers and coordinating center and record keeping system to track data acquisition
- Establishment of collaboration with Pediatric Brain Tumor Consortium to conduct clinical trials of farnesyl transferase inhibitor and angiogenesis inhibitor for plexiform neurofibromas

It should be noted here that there has been one significant unanticipated challenge, involving army IRB approval of the informed consents used by all participating centers. Army review of the consent forms occurred very slowly in the winter and early spring of 1999, largely due to staff turnover at the MCMR; indeed for a significant period of time we were not able to receive updates on the progress of IRB approval at all. The process has subsequently moved very slowly, often with forms going back and forth over a period of many months between the army IRB and local IRB's. In some cases, centers were informed that they would be approved by one staff member, only to be told that they were not approved weeks later by a different staff member. We have found that, once approval is granted, subject recruitment goes quickly and smoothly (recruitment at Children's Hospital was completed within about 6 weeks). The process of IRB approval is nearing completion, but this delay will require us to extend the study period by 6-12 months. There should be sufficient unexpended funds related to cover the costs of this extension, due to the reduced level of clinical activity during this first year.

CONCLUSIONS

The infrastructure for the study is now completed, and data transfer has been tested. The first MRI data has been received at WorldCare, and the study of reproducibility of volumetric analysis is now underway. Although subject recruitment has been delayed because of difficulties with IRB approval, this obstacle is mostly resolved, and we are confident that subject recruitment will be completed over the next 6 months.

Attachment A

NATURAL HISTORY OF PLEXIFORM NEUROFIBROMAS IN NF1

PROCEDURES AND POLICIES MANUAL

Version 3.00

May 13, 1999

Section A

Table of Contents

Appendices

Section B

Introduction

This manual provides a description of procedures and policies for participants in the project "Natural History of Plexiform Neurofibromas in NF1" supported by the U.S. Army. The contents are subject to approval and revision by the executive committee of the project. Questions or comments should be directed to:

Principal Investigator:

Bruce R. Korf, M.D., Ph.D.
Division of Genetics
Children's Hospital
300 Longwood Ave.
Boston, MA 02115
Phone: 617-355-6091
Fax: 617-355-7588
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project home page:

Study Coordinator:

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Overview and Goals of Project

This is a four-year study, the overall objective of which is to set up a system that will facilitate clinical trials of potential therapies for plexiform neurofibromas in NF1. These tumors are unpredictable in terms of rate of growth and are difficult to measure. We will set up a network of clinical centers and will follow the growth of plexiform neurofibromas using volumetric MRI. These centers will be supported by a tissue bank, in which tissue samples will be made available to investigators throughout the world. In addition there will be a database used to track clinical information about patients with NF1 and a standard pathology review for any biopsy material. The first stage of this project will involve setting up the infrastructure. Subject recruitment will begin in April 1999. The study will then continue over a three-year period, during which patients will be present for clinical assessments and MRIs. The protocol includes an algorithm for determination of the time for repeat MRI's; clinical assessments will occur at 6 monthly intervals. The last six months of the study will be devoted to data analysis.

Study Objectives

A. Determine the efficacy of volumetric MRI for measurement of the growth rate of plexiform neurofibromas.

B. Provide a body of normative data on the growth rate of plexiform neurofibromas. Although limited by a relatively short study period, the following hypotheses will be tested:

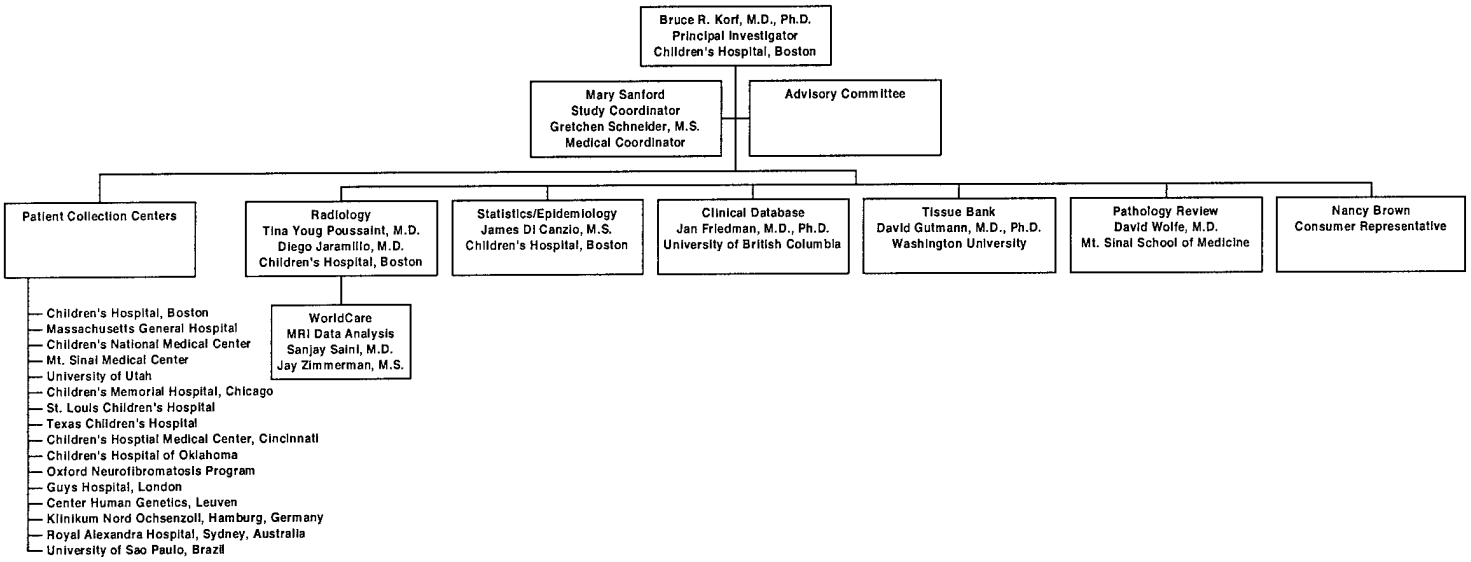
i) Most plexiform neurofibromas grow out of proportion with somatic growth for a period of time during childhood but reach a plateau by the end of puberty;

ii) Patterns of neurofibroma growth may vary from patient to patient but there are no systematic differences in growth patterns according to location of the neurofibroma in the body;

C. Establish a consortium of clinical centers supported by a tissue repository and central review of pathology, radiology, and statistical data.

Organizational Structure

Study of Natural History of Plexiform Neurofibromas in NF1



Section C

Administration

Principal Investigator

Bruce R. Korf, M.D., Ph.D.
Children's Hospital and Harvard Medical School, Boston

Executive Committee

Bruce R. Korf, M.D., Ph.D.
Gretchen Schneider, M.S.
Mary Sanford
Tina Young Poussaint, M.D.
Diego Jaramillo, M.D.
Jim DiCanzio, M.S., Ph.D.
Jay Zimmerman, M.S.
David Gutmann, M.D., Ph.D.
David Wolfe, M.D., Ph.D.,
Jan Friedman, M.D., Ph.D.
Nancy Brown

Participating Centers

Please see Appendix A

Publication Policy

A report of the study of MRI volumetric data will be prepared by the principal investigator, radiologists, and statistician, with the members of the consortium listed as co-authors. Other papers may be prepared by any member of the consortium using data from their own patients, or data from patients at other centers with the permission of the relevant investigators.

Section D

Subject Recruitment

Entry Criteria

A. Diagnosis of Neurofibromatosis: All study subjects will fulfill diagnostic criteria for NF1.

i) Six or more *café-au-lait* macules
   a. 1.5cm or larger in postpubertal individuals
   b. 0.5 cm or larger in prepubertal individuals

ii) Two or more neurofibromas of any type *or* 1 or more plexiform neurofibroma

iii) Freckling in the axilla or groin

iv) Optic glioma (tumor of the optic pathway)

v) Two or more Lisch nodules (benign iris hamartomas)

vi) A distinctive bony lesion
   a. Dysplasia of the sphenoid bone
   b. Dysplasia or thinning of long bone cortex

vii) A first degree relative with NF-1

B. Plexiform Neurofibroma: A plexiform neurofibroma fulfilling entry criteria for the study will be defined as a diffuse soft tissue or nerve enlargement in a patient with NF1 that is causing or has potential to cause disfigurement or functional disability.

C. Distribution of Plexiform Neurofibromas by site: A total of 300 plexiform neurofibromas will be studied, consisting of 100 tumors in the following three groups (based on region of maximal involvement):

1. **Head and Neck**
2. **Trunk and Limbs (externally visible)**
3. **Trunk and Limbs (internal) [spinal plexiform neurofibromas involve two or more levels with connection between the levels or extending laterally along the nerve]**

D. **Subject Ascertainment:** Study subjects will be ascertained at any of the participating clinical centers. It is expected that these will include subjects already followed in these clinics, as well as newly diagnosed patients.

E. **Exclusion Criteria:** Exclusion criteria will be:

i) Presence of metallic implant that will make the patient unable to have MRI studies

ii) Presence of medical or psychological condition that will make the patient unable to tolerate MRI studies or anesthesia (if needed)

iii) Inability to image tumor or define tumor margins by MRI (which may be determined after the initial study)

iv) Failure to obtain initial MRI within 60 days of enrollment

v) Previous radiation therapy to site of plexiform neurofibroma

vi) Surgery involving the plexiform neurofibroma (excluding biopsy) within a six month period before enrollment

vii) Current antineoplastic therapy

Informed Consent

The protocol has been approved by the U.S. Army IRB and the Children's Hospital, Boston IRB. Each PCC is responsible for obtaining approval from its respective IRB. The informed consents from Children's Hospital are in Appendix B. It is expected that similar forms will be used at each PCC, with only minor institution-specific changes.

US Army Volunteer Registry Database

The information is used to respond to Freedom Information Act requests for information by a subject of his or her participation in research sponsored by our Command. We also maintain the VRDB to ensure that we can, if necessary, provide new information to individual subjects regarding their participation in a DOD sponsored study. Access to the information maintained in the VRDB is restricted and is protected by the Privacy Act of 1974. The Privacy Act provides for criminal penalties for unauthorized use or release of information.

Every participant must fill out the Volunteer Registry Data Sheet (Appendix C). The form is to be mailed directly to the US Army. Do NOT send the form to Children's Hospital.

Registration

Subjects will be registered in the study when the clinical coordinator from a PCC calls the study coordinator at Children's Hospital, Boston and provides a completed Subject Registration Form (Appendix D). The Medical Coordinator and the Principal Investigator will review the subject information. Subjects will be admitted to the study if entry criteria are fulfilled, no exclusion criteria are met, and there is an appropriate opening in the study in one of the six groups based on subject age and location of the plexiform neurofibroma. It is not permissible for a single subject to be entered into more than one study group, if more than one plexiform neurofibroma is present. It is also not permissible for multiple members of the same family to be entered into the study.

Withdrawal from Study

Subjects may withdraw voluntarily from the study at any time, or may be dropped from the study due to non-participation. Non-participation will be defined as being more than 3 months late for a scheduled clinical or radiological follow-up. Subjects who have surgery on the plexiform neurofibroma other than biopsy or antineoplastic therapy will be excluded from data analysis, but may continue to have volumetric analysis of MRI data at the discretion of the steering committee, with the data segregated from other subjects. A Subject Withdrawal Form (Appendix E) should be provided to the Principal Investigator.

Subject Reimbursement

There is no provision to reimburse subjects for participation in the study.

Adverse Events

Adverse events related to the study must be reported within 72 hours to the Principal Investigator using the Adverse Events Report Form (Appendix F).

Section E

A. Timing

Patient visits will occur every 6 months, some including **only** a clinical assessment, others including **both** a clinical assessment and a MRI.

B. Clinical Assessments

Procedures for collection and transmission of clinical data are located in Section F.

C. MRIs

Procedures for collection and transmission of MRI data are located in Sections G & H.

Section F

Clinical Assessment Protocol

Timing

Each study subject will receive a complete physical examination at the start of the study, and at intervals of every 6 months during the three year study period. Subjects will be seen whether or not an MRI is scheduled.

Clinical Evaluation and Data Entry

Clinical evaluations will be performed by the physician associated with each PCC. Standard physical examination will be done, and the clinical data entry form will be filled in (Appendix H). Instructions for using the International Database are located in Appendix G. A copy of the clinical data form will then be sent to Children's Hospital, Boston, which will then forward the form to University of British Columbia for entry into the computer database.

Measurements

Plexiform neurofibromas visible on the surface will be measured both with a tape measure and/or with calipers. At least two measurements, representing largest diameters along two perpendicular lines, will be taken. Multiple measurements will be done for irregularly shaped tumors, as necessary. Landmarks will be recorded by the clinician to ensure that measurements are made in a consistent manner from visit to visit.

Photography

Plexiform neurofibromas that are visible on the body surface will be photographed every six months at the time of clinical evaluation. Photography will be done using a 35 mm camera using Ektachrome 100 film or equivalent. A size marker will be taped to the skin in the field of view, and the neurofibroma will be photographed so that it fills the frame. Frontal and side images will be taken, as appropriate. Copies of photographs will be sent to the study coordinator, identified by the subject ID number.

Section G

MRI Protocol

Timing of MRI

All subjects will have an MRI done at the time of recruitment into the study, at one year, and at three years. Additional scans may be done at the discretion of the physician for clinical indications.

Arrangements for MRI

MRI scans will be scheduled by the PCC clinical coordinator using the MRI scanner at the PCC. The clinical coordinator will notify Mary Sanford at Children's Hospital, Boston of the anticipated date of the MRI and will notify the radiology technologist of the study protocol.

Payment for MRI

The costs of MRI will be billed to patient's insurance. Limited funds are available to cover the cost of MRI's for patients who do not have insurance, or for those in whom insurance coverage is denied. Reimbursement for MRI will only be done at a research rate and will require prior approval by the Principal Investigator. The form to request reimbursement for MRI by the study is in Appendix J.

MRI Acquisition Protocol

See Appendix M

Please Note: The MRI acquisition protocols are separated into Head/Neck, Trunk and Extremities, and Spine. These differ from the three classes of subjects recruited into the study. The MRI protocol to be used depends on the anatomical location of the plexiform neurofibroma, and should be reviewed by the clinician and radiologist doing the study.

Section H

WorldCare, Inc.

Introduction:

WorldCare, Inc. has developed these Standard Operating Procedure (SOP) Guidelines in support of the Neurofibromatosis 1 Study. This manual supports the operations and data tracking of the **Patient Collection Centers**. This support is required until the conclusion of the Neurofibromatosis 1 Study, as determined by The United States Army Research and Material Command.

Prior to the collection of any study data, each Patient Collection Center should complete the WorldCare Site Survey in Appendix K. A completed copy of this survey must be forwarded to WorldCare before any actual study data can be accepted.

Proprietary Statement:

Disclaimer:

WorldCare
Global Clinical Trials

MRI Data Collection Procedure

Responsibility: PCC Technician, PCC Clinical Coordinator

Requirements: Data Collection Form (Appendix L), Acquisition Protocol (Appendix M)

Definition The Data Collection Procedure (DCP) outlines the steps used to capture patient and visit information and MRI data. In this procedure, the Patient Collection Center (PCC) technician acquires information that will be transferred to either Children's Hospital by optical disk or to the WorldCare Measurement Center (WC-MC) by FTP. The PCC technician should perform the series indicated by the NF1 Acquisition Protocol in addition to the normal clinical scan if it is not already included.

> *Note: The standard phantom calibration will be performed each morning prior to any data acquisition to ensure scanner is functioning within normal operating parameters.*

Start Procedure

Baseline visits:

1. Patient ID #s will be assigned by the NF1 Research Coordinator, Mary Sanford, at Children's Hospital when patients are registered. This ID # must be used for **all follow-up** scans. After an ID number has been assigned, the PCC Clinical Coordinator will contact CH with the date that the patient will be scanned.

2. Gather materials identified in this procedure's requirements listed above. Record all relevant information on the Data Collection Form in the appropriate spaces.

3. Follow the NF1 Acquisition Protocol used to perform each scan. If there are any changes to the NF1 Acquisition Protocol, please record the change and the reason for the change in the space provided.

> The PCC Technician must sign both the NF1 Acquisition Protocol and the DCF before it is sent to Children's Hospital. The PCC Clinical Coordinator must also sign the acquisition protocol.

4. Send the signed originals of the NF1 Acquisition Protocol and Data Collection Form (DCF) to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital.

Follow-up visits:

1. Gather materials identified in this procedure's requirements listed above. Record all relevant information on the Data Collection Form in the appropriate spaces.
2. Follow the NF1 Acquisition Protocol used to perform each scan. If there are any changes to the NF1 Acquisition Protocol, please record the change and the reason for the change in the space provided.

> The PCC Technician must sign both the NF1 Acquisition Protocol and the DCF before it is sent to Children's Hospital. The PCC Clinical Coordinator must also sign the acquisition protocol.

3. Send the signed originals of the NF1 Acquisition Protocol and Data Collection Form (DCF) to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital.

> If the scanner software or hardware is upgraded during the course of the study for the follow up visits, the PCC technician is encouraged to perform additional scans to test the variability between the old and new scanners. Additional scans with improved quality will benefit the data extracted.

File Transfer Protocol (FTP) Procedure ***(Preferred Method of Data Transfer)***

Responsibility: PCC Technician, PCC Clinical Coordinator
Requirements: Data Collection Form, Signed Acquisition Protocol

Definition The File Transfer Protocol procedure completes the patient collection process by transferring images to WCMC and notifying CH that patient images have been acquired and are being shipped. Copies of the Data Collection Form and signed Acquisition Protocol are sent to CH. This procedure also records data tracking and the activities associated with the movement of information between the PCC and CH.

Start Procedure

1. Gather materials identified in this procedure's requirements.
2. Make a copy of the Data Collection Form and the signed Acquisition Protocol and file them in patient file. The ***original*** DCF form and signed Acquisition Protocol should be sent to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital.
3. To transfer data:
   a) Start FTP Client (WS_FTP95 LE on Windows NT/95, XFTP on Unix or Fetch on Macintosh)
   b) Log into host252.ct.worldcare.com
      - For Host name/address, enter host252.ct.worldcare.com
      - For Host type, enter "automatic detect"
      - For User ID, enter NF1
      - For password, enter NF1
   c) Select "binary" mode
   d) Navigate to NF1 directory
   e) Create a directory PATID_VISIT# to transfer
   f) Select files under local system and transfer to remote system by selecting the appropriate arrow button

Data Archival and Optical Disk Shipment Procedures *(Alternative Method)*

Responsibility: PCC Technician, PCC Clinical Coordinator

Requirements: Optical Disk, Data Collection Form, Signed Acquisition Protocol

Note: WorldCare's preferred data transfer method for the Neurofibromatosis 1 study is FTP. If the site(s) have the capacity (i.e. passage through a firewall, internet connectivity) to transfer data electronically to WC, the FTP procedure should be used.

Definition The Data Archival and Optical Disk Shipment Procedure archives the acquired patient images onto optical disk and forwards the optical disk package to CH. This procedure will produce an original hard copy output for each set of patient images on optical disk. This output is packaged and sent to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital. A copy of the Data Collection Form and the signed NF1 Acquisition Protocol are forwarded to CH along with the optical disk. This procedure also records data tracking and the activities associated with the movement of information between the PCC and CH.

The optical disk used for this procedure is a WORM disk provided to the Clinical Coordinator by the WC-MC. However, the disk will only be provided if the PCC is unable to perform the FTP procedure. ***For further description of WORM, see explanation below.***

Start Procedure

1. Gather materials identified in this procedure's requirements. All relevant patient information should be recorded on the optical disk label for archiving purposes.
2. Produce an original hard copy output of the data set.
3. Each WORM disk will have two labels. One label at the top of the disk and a different label for the side of the disk.
   a) The top of the disk (the label visible when the optical disk is in its cover) will already be labeled by the WC-MC technician in the following manner:

   The PCC Clinical Coordinator should confirm that the disk is labeled properly.

Example:	NF1	=	Study Abbreviation
	MGH	=	Facility initials (see Associated Acronyms)
	A or B	=	Side of disk which contains data
	#	=	Disk Number (1=first, 2=second, 3...)
Final Label:	NF1-MGH-A-D2		

b) The PCC Clinical Coordinator must fill in the side label for each patient visit stored on the disk. The side label of the optical disk (the label on each side of the disk) should indicate which patients are included on each disk and the patient visit number.

Example:	123-4321-567	=	Patient ID number
	V1/25/99	=	Visit Date
Side Label:	123-4321-567-V1/25/99		

The PCC Clinical Coordinator should confirm that the disk is labeled properly.

4. Complete the Data Collection Form with the required patient information and shipping information. Include the DHL shipping number and the date the optical will be shipped.
5. Place one copy of the Data Collection Form in the Patient Study File stored at the PCC.
6. Place one copy of the signed Acquisition Protocol in the Patient Study File stored at the PCC.
7. Ship the optical disk along with the originals of the Data Collection Form and the signed Acquisition Protocol to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital. The copies of the DCF form and the signed NF1 Acquisition Protocol should be filed at the PCC in the Patient Study File.

The PCC Clinical Coordinator must review all documentation before filing at the PCC and sending to CH. The PCC Clinical Coordinator is also responsible for tracking all packages shipped and received for the purposes of the NF1 Study.

WORM Optical Disk Explanation

For each patient visit, the assigned Clinical Coordinator at each PCC will provide the optical disks at the time of each scan. The type of optical disk used for the transfer and archival of patient data is a WORM (Write Once Read Many) optical disk. The patient data on this disk can not be written over. However, the disk may be used for other patient visits if there is additional space left on the optical disk following each visit (approximately 4-5 visits per disk). Therefore each site will be provided with an optical disk that may be shipped to Children's Hospital following a patient visit and then returned to the site once the data has been entered in to the database at WorldCare. These disks will act as carriers of patient data for the NF1 study and each disk will be used until it runs out of space. When the WC-MC receives a full optical from the PCC, the WC-MC will ship a new empty disk to the Clinical Coordinator, at the PCC.

Section I

Plexiform Neurofibroma Tumor Repository

Introduction

The Washington University Tumor Repository Core will process whole blood from aliquots of peripheral leukocyte cell pellets. Tissue and white cell pellets will be stored along with basic patient identifiers and data in the Repository Core Facility. The Washington University Department of Neurology will be billed for procurement services on a per specimen basis. The Repository will also bill for a yearly specimen storage fee.

Genomic DNA, RNA, cDNA, protein lysates, and histological sections from collected material will be made available to investigators after appropriate panel review. There will be a nominal specimen processing charged billed to each requesting investigator for samples distributed.

Instructions for Sample Collection

1. Three to five days prior to tumor resection, please call or fax Ms. Louise Burrell at the Washington University Cancer Center Tumor Repository. Provide the name and shipping address of the physician (probably a pathologist) responsible for tissue acquisition.

   Phone: **314-454-7919**
   Fax: **314-454-5525**
   24 hr Pager: **314-424-9106**

2. A shipping module will be mailed via overnight express to the physician indicated.

3. At the time of resection, tissue should be IMMEDIATELY transported from the operating room to the attending surgical pathologist. Material not needed for clinical management should be cut into pieces less than 1 cm^3 in size, placed in the appropriately labeled specimen bag, and IMMEDIATELY snap frozen in liquid nitrogen or -50 degree histology cryobath. Once frozen, the tissue may be maintained in the cryobath or a -70 degree freezer until it is ready for shipment. It is very important that: (1) Tissue be frozen as soon as possible after resection; (2) Tissue be frozen rapidly; and (3) Tissue be maintained at or below -50 degrees until shipment.

4. If possible, please collect 20 cc of blood from each patient in purple top (NaEDTA) tubes. From each parent, please collect 20 cc of blood in purple top (NaEDTA) tubes. Label all tubes with patient's name and/or parent's relationship to patient. Store blood at 4 degrees until shipping. **DO NOT FREEZE THE BLOOD.**

Shipping Instructions

Shipping modules will be mailed via overnight express to the physician indicated by Louise Burrell.

Please call Ms. Louise Burrell at The Washington University Cancer Center at (314) 454-7919 prior to shipping.

Do not send specimens on Friday or the day preceding a holiday. Store samples until Monday at the appropriate temperature.

Blood

1. Samples should be sent at room temperature. They need to be carefully wrapped to protect them from breakage. All shipments are sent priority one.

2. Label all tubes of blood with NF Patient ID # and/or relation to patient.

Tissue Sample

1. Label all sample packaging with NF Patient ID #.

2. Add ~8 lbs. of dry ice to shipping container and bury plastic bags containing tissue specimens in the dry ice. Cover the tissue / dry ice with the foam insulator. Remember to include completed patient data form. Seal shipping container and affix pre-printed shipping label.

Contact

Mark A. Watson M.D., Ph.D.
Assistant Professor of Pathology
Division of Laboratory Medicine / Box 8118
Washington University School of Medicine
660 S. Euclid Ave.
St. Louis, MO. 63110
Phone: (314) 454-7919
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Appendix A

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Appendix B

CHILDREN'S HOSPITAL
BOSTON, MASSACHUSETTS
ADULT PARTICIPANT INFORMED CONSENT

Participant's Name: _____ Date: _____

Project Title: Natural History of Plexiform Neurofibromas

Protocol Number: 97-12-239

(Dates are modified by the Clinical Investigation Office only.)

Consent Form Valid from June 14, 1999 through June 13, 2000

DESCRIPTION AND EXPLANATION OF PROCEDURE:

We are asking for your consent for you to participate in a research study of the rate of growth of plexiform neurofibromas. Plexiform neurofibromas are a particular type of benign tumor that occurs in persons with neurofibromatosis type 1. The growth patterns of these tumors appear to be unpredictable and the factors that influence that growth are largely unknown. The goal of this study is to closely monitor the growth of plexiform neurofibromas for a period of at least three years using magnetic resonance imaging (MRI). This technique will permit us to measure the overall size (volume) of the plexiform neurofibroma. By repeating the assessment every 6-24 months we hope to be able to document the rate of change in size of the plexiform neurofibroma. This is part of an international study in which 300 individuals with NF1 will be enrolled; here at Children's Hospital we plan to enroll approximately 20 – 30 people.

Participation in this study will involve both clinical assessment and MRI scanning. The clinical assessment will occur every six months for three years. This will take place at Children's Hospital on Fegan 10 in the Neurofibromatosis Clinic. A standard physical examination will be done, the same as for a standard clinic visit. If the plexiform neurofibroma is visible on the surface it will be measured with a ruler or tape measure and photographs will be taken. Since these visits are deemed part of your clinical care, they will be billed to your medical insurance as standard clinical visits. A clinic note will be placed in the medical record and copies sent to your primary care provider, as is standard in the clinic. Data about your clinical assessment will be entered into a computer database. This clinical data is also sent to a central database maintained by the University of British Columbia, sponsored by the National Neurofibromatosis Foundation. You will be identified in this central database only by a code number, but not by name, to preserve confidentiality. Photographs of your plexiform neurofibroma will be kept in a confidential file in the Division of Genetics. Clinic visits will occur over a period of 30-45 minutes.

At the time of the first clinic visit when this study begins a blood sample will be obtained from you. The blood sample will be drawn from a vein in the arm, and will consist of approximately 5 – 10 cc (1 – 2 teaspoons). This sample will be used as a source of DNA, the genetic material inside our cells. We will also obtain serum (the liquid component of blood). This DNA and serum will be sent to a central tissue repository at Washington University in St. Louis and banked there. There are no immediate plans to study this DNA and serum, but at some point in the future it may be possible to examine the DNA for the changes in the NF1 gene, or in other genes that may alter the behavior of neurofibromas. The serum may be used to test for substances in the blood that cause neurofibromas to grow. Since we will be monitoring the growth of the neurofibroma carefully, we hope to have the opportunity to examine genetic or serum factors that may influence tumor growth at some point in the future. There is no assurance, however, that such testing will be possible or necessarily will be done. Any results obtained from DNA or serum studies will be kept confidential. You will have the opportunity to designate whether you would like to learn the results of such testing in the future, and whether you would like us to share these results with any health providers whom you designate. You can direct us to withdraw the blood sample from the repository at any time.

MRI scanning of the plexiform neurofibroma will be part of this study. Every participant will have an MRI at the time of enrollment into the study (unless the plexiform neurofibroma has been followed by MRI for a period of time before the study and is known to have not changed in size). A second MRI will be done one year later unless there are clinical reasons to do it sooner. MRI will be repeated at the end of the study, at three years. If the neurofibroma appears to be growing, either based on clinical assessment or from measurements of the MRI scans, follow-up MRI may be done more often, at the discretion of your physician, in accordance with standard clinical care.

In most cases these MRI scans are used in standard clinical care and will therefore be billed to your insurance. There may be some instances in which an MRI might not have been performed for routine clinical purposes at the same time as designated by the study. In these cases, funds are available to defray the costs of the MRI scan. In some instances it will be necessary to use sedation or general anesthesia. Consent for this procedure will be obtained by the radiologist or anesthesiologist prior to the procedure. Also, in some cases, it will be necessary to insert an intravenous line and administer contrast material into the vein. This will be done at the discretion of the radiologist, if it appears that contrast is necessary to better visualize the neurofibroma. Your consent will be obtained prior to this procedure. We expect that the MRI scans will require approximately one hour.

We do not plan to perform surgery or take a sample of the plexiform neurofibroma as part of this study, but in some cases surgery may be performed because of clinical indications. This decision will not be influenced by your

participation in the study, and will not affect your participation in the study. If there is neurofibroma tissue available that is not needed for examination as part of clinical care, this tissue will be collected and sent to a central tissue bank at Washington University in St. Louis. In addition, a sample will be sent to Mt. Sinai School of Medicine for review of the pathological features of the neurofibroma. The tissue will be identified with a code number, and will only be possible to connect with your name through our clinic. The tissue may be distributed to investigators to help with their research on neurofibromatosis. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. It is not anticipated that results of study of your neurofibroma tissue will influence clinical management, and therefore you will not be informed of research results on this tissue. All research results will be kept confidential. You can withdraw your specimen from the tissue repository at any time.

RISKS AND DISCOMFORTS:

1. Clinical Assessment: The clinical assessments will be the standard ones performed in our Neurofibromatosis Clinic, with the addition of measurement of any visible plexiform neurofibroma. This assessment may cause some embarrassment, anxiety, and inconvenience. We will make every effort to insure that the clinic visits occur in an efficient and dignified manner, and will make every effort to explain what is being done and what is found. The clinic visits will be billed as standard clinical assessments. We will obtain prior approval from your insurance company and to explain that clinical follow-up of plexiform neurofibromas is appropriate clinical care.

2. Photography of Plexiform Neurofibromas: The photographs will be taken only of the region of your body affected by the plexiform neurofibroma. These photographs will be kept in a confidential file and will not contain your name. In some cases they may be used for teaching purposes or in scientific or medical publications related to this work, however.

3. Clinical Database: The clinical database is kept on a computer in a password-protected file. There is a potential risk of your clinical information being read by unauthorized persons, although the use of a password system should minimize this risk. To preserve your privacy, any data sent to the central database will be sent without any personal identifying information. You will be identified in the central database only by a code number, and our clinic will be the only place where the code number can be linked to your name.

4. Blood Sampling: The blood sampling procedure involves insertion of a needle into a vein in the arm and withdrawing 5 – 10 cc of blood (1 – 2 teaspoons). We expect to take no more than 10 cc (2 teaspoons) from adults. There is discomfort associated with blood drawing, and very slight risk of infection due to insertion of the needle. There is also risk of redness, bruising, and swelling

at the site from which the blood is removed. Blood will be drawn in the Children's Hospital phlebotomy (blood drawing) center, and every effort will be made to minimize the pain and to obtain the blood using sterile procedures.

5. Genetic Studies: Although there is no immediate plan to perform genetic studies from the blood samples obtained, genetic material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that DNA samples will be stored indefinitely in this repository. The sample will be identified by a code number that can be traced to you only by contact with our clinic. Genetic testing may eventually reveal the neurofibromatosis gene mutation that is responsible for NF1 in you. Although genetic testing can, in some cases, result in discrimination for health or life insurance or employment, we believe that these risks are minimal since it is already known that you have neurofibromatosis. It may also be possible to examine other genes that may influence the growth of neurofibromas in persons with NF1. Some of these may be genes that themselves can have implications for health. You will be given an opportunity to indicate whether you wish to know about any results that may be obtained, and whether you would like us to share these results with your health provider. We will keep all results confidential, however, and not disclose them to any other individual without your permission.

6. Tumor Studies: Tumor material will be obtained only if surgery is indicated for clinical reasons, and only after the pathologist and surgeon have determined that any material necessary for clinical care has been obtained. We will not ask that additional tumor material be obtained solely for research purposes, and will confine any tissue saved for research purposes to any excess tumor available after clinical studies are completed. Although there is no immediate plan to perform studies from any tumor samples obtained, tumor material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that the tissue samples will be stored indefinitely in the repository. The sample will be identified by a code number that can be traced to you only by contact with our clinic. No results will be placed in your medical record or disclosed to anyone without your permission.

7. MRI: Magnetic resonance imaging (MRI) is a standard procedure used for imaging plexiform neurofibromas. There are no known or foreseeable risks associated with exposures to MRI provided no metal implanted prostheses (*e.g.,* vascular clamps or pacemakers; braces are not a problem). All potential subjects will be screened for the presence of such prior to the examination. Some participants in the study may require sedation or anesthesia to perform MRI. Consent for this will be obtained prior to the study. It must be recognized that there are risks associated with sedation and

anesthesia, including the risk of death in rare instances. The MRI scans and sedation/anesthesia costs will be billed to insurance.

POTENTIAL BENEFITS:

This study is being performed in conjunction with routine clinical care. It is standard to see individuals with neurofibromatosis in clinic at least once per year and more often if there is a problem such as plexiform neurofibroma. MRI imaging of plexiform neurofibromas is also done as part of standard clinical care. It is possible that, in the course of this study, growth of a plexiform neurofibroma will be discovered that requires further treatment, most likely surgical. In that case, referral to a surgeon who is familiar with the management of plexiform neurofibromas will be made. The MRI data in this study will be analyzed by a special approach called "volumetric MRI," in addition to being read in a standard manner by a radiologist. It is expected that the volumetric MRI approach will provide more precise measurement of the size of plexiform neurofibromas, and therefore will give more complete and objective information on which to base any possible future treatment decisions. Volumetric MRI is currently not available on a routine clinical basis.

ALTERNATIVES:

If you chose not to participate in this study, it will not influence your care or management in the Neurofibromatosis Program. It may be deemed necessary for you to have routine clinical assessments for a plexiform neurofibroma, which may include MRI scanning, but this will be done outside the context of the research study if you choose. This means that the data will not be shared with the central data facility and that DNA and potential tumor samples will not be obtained. Otherwise your care will be the same.

VOLUNTEER REGISTRY DATA BASE REQUIREMENTS:

This study is supported by the U.S. Army. It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number (if US Citizen), study name, and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risk and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

MEDICAL CARE FOR RESEARCH RELATED INJURY:

Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

REVIEW OF RESEARCH RECORDS:

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

CONSENT:

I have fully explained to _____ the nature and
Participant
purpose of the above-described procedures and the risks involved in their performance. I have answered and will answer all questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits if any should occur during or after the course of the study. I have given a copy of the consent form to the subject.

_____ _____
Date Investigator's and/or Associate's Signature

CONSENT:

I have been satisfactorily informed of the above-described procedure and with its possible risks and benefits. I give permission for my participation in this study. I know that Dr. Korf or his associates may be reached at (617) 355-6394 and will be available to answer any questions that I may have. If I have questions regarding my rights as a research subject or questions regarding compensation in the event of a research related injury, I may request to speak with a member of the Hospital Consent Committee by calling (617) 355-7052. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect my care. I have been given a copy of this form.

I understand that there is a possibility that the blood, tissue, body fluid, or sample(s) of neurofibroma tissue that I am providing under this study may also be used in other research studies and could potentially have some commercial applicability.

_____ _____

Date Signature of Patient/Participant

Name of Participant _____

Address of Participant _____

_____

_____ _____

Date Witness to Signatures

Name of Witness _____

Address of Witness _____

_____

6/14/99

Disclosure of Information Obtained from Genetic Studies

Please indicate whether you wish to be informed of any results of genetic studies that may be relevant to your health or to genetic counseling of you or your family:

I wish to be informed of the results of any genetic tests performed on my/my child's blood or tumor tissue that may have implications for health care or genetic counseling.

I do not wish to be informed.

Please indicate the name and address of any health provider to whom you would like any results sent.

Name: _____

Address: _____

City: _____

State: _____ Zip: _____

6/14/99

Sample Donation Form

Natural History of Plexiform Neurofibromas in NF1

I voluntarily and freely donate any and all blood, tissues, body fluid, product, or sample(s) of neurofibromas to Children's Hospital and hereby relinquish all right, title, and interest to said items.

_____ _____

Date Signature of Patient/Participant

Name of Participant _____

Address of Participant _____

_____

_____ _____

Date Witness to Signatures

Name of Witness _____

Address of Witness _____

_____

6/14/99

CHILDREN'S HOSPITAL
BOSTON, MASSACHUSETTS
CHILD PARTICIPANT INFORMED CONSENT

Participant's Name: _____ Date: _____

Project Title: Natural History of Plexiform Neurofibromas

Protocol Number: 97-12-239

(Dates are modified by the Clinical Investigation Office only.)

Consent Form Valid from June 14, 1999 through June 13, 2000

DESCRIPTION AND EXPLANATION OF PROCEDURE:

We are asking for your consent for your child to participate in a research study of the rate of growth of plexiform neurofibromas. Plexiform neurofibromas are a particular type of benign tumor that occurs in persons with neurofibromatosis type 1. The growth patterns of these tumors appear to be unpredictable and the factors that influence that growth are largely unknown. The goal of this study is to closely monitor the growth of plexiform neurofibromas for a period of at least three years using magnetic resonance imaging (MRI). This technique will permit us to measure the overall size (volume) of the plexiform neurofibroma. By repeating the assessment every 6-24 months we hope to be able to document the rate of change in size of the plexiform neurofibroma. This is part of an international study in which 300 individuals with NF1 will be enrolled; here at Children's Hospital we plan to enroll approximately 20 – 30 people.

Participation in this study will involve both clinical assessment and MRI scanning. The clinical assessment will occur every six months for three years. This will take place at Children's Hospital on Fegan 10 in the Neurofibromatosis Clinic. A standard physical examination will be done, the same as for a standard clinic visit. If the plexiform neurofibroma is visible on the surface it will be measured with a ruler or tape measure and photographs will be taken. Since these visits are deemed part of your child's clinical care, they will be billed to your child's medical insurance as standard clinical visits. A clinic note will be placed in the medical record and copies sent to your child's primary care provider, as is standard in the clinic. Data about your clinical assessment will be entered into a computer database on a computer in the Division of Genetics. This clinical data is also sent to a central database maintained by the University of British Columbia, sponsored by the National Neurofibromatosis Foundation. Your child will be identified in this central database only by a code number, but not by name, to preserve confidentiality. Photographs of your child's plexiform neurofibroma will be kept in a confidential file in the Division of Genetics. Clinic visits will occur over a period of 30-45 minutes.

At the time of the first clinic visit when this study begins a blood sample will be obtained from the study participant (*i.e.,* your child). The blood sample will be drawn from a vein in the arm, and will consist of approximately 5 – 10 cc (1 – 2 teaspoons). This sample will be used as a source of DNA, the genetic material inside our cells. We will also obtain serum (the liquid component of blood). This DNA and serum will be sent to a central tissue repository at Washington University in St. Louis and banked there. There are no immediate plans to study this DNA and serum, but at some point in the future it may be possible to examine the DNA for the changes in the NF1 gene, or in other genes that may alter the behavior of neurofibromas. The serum may be used to test for substances in the blood that cause neurofibromas to grow. Since we will be monitoring the growth of the neurofibroma carefully, we hope to have the opportunity to examine genetic or serum factors that may influence tumor growth at some point in the future. There is no assurance, however, that such testing will be possible or necessarily will be done. Any results obtained from DNA or serum studies will be kept confidential. You will have the opportunity to designate whether you would like to learn the results of such testing in the future, and whether you would like us to share these results with any health providers whom you designate. You can direct us to withdraw the blood sample from the repository at any time.

MRI scanning of the plexiform neurofibroma will be part of this study. Every participant will have an MRI at the time of enrollment into the study (unless the plexiform neurofibroma has been followed by MRI for a period of time before the study and is known to have not changed in size). A second MRI will be done one year later unless there are clinical reasons to do it sooner. MRI will be repeated at the end of the study, at three years. If the neurofibroma appears to be growing, either based on clinical assessment or from measurements of the MRI scans, follow-up MRI may be done more often, at the discretion of your child's physician, in accordance with standard clinical care.

In most cases these MRI scans are used in standard clinical care and will therefore be billed to your child's insurance. There may be some instances in which an MRI might not have been performed for routine clinical purposes at the same time as designated by the study. In these cases, funds are available to defray the costs of the MRI scan. In some instances, particularly for small children, it will be necessary to use sedation or general anesthesia. Consent for this procedure will be obtained by the radiologist or anesthesiologist prior to the procedure. Also, in some cases, it will be necessary to insert an intravenous line and administer contrast material into the vein. This will be done at the discretion of the radiologist, if it appears that contrast is necessary to better visualize the neurofibroma. Your consent will be obtained prior to this procedure. We expect that the MRI scans will require approximately one hour.

We do not plan to perform surgery or take a sample of the plexiform neurofibroma as part of this study, but in some cases surgery may be performed because of clinical indications. This decision will not be influenced by your child's participation in the study, and will not affect your child's participation in the study. If there is neurofibroma tissue available that is not needed for examination as part of clinical care, this tissue will be collected and sent to a central tissue bank at Washington University in St. Louis. In addition, a sample will be sent to Mt. Sinai School of Medicine for review of the pathological features of the neurofibroma. The tissue will be identified with a code number, and will only be possible to connect with your name through our clinic. The tissue may be distributed to investigators to help with their research on neurofibromatosis. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. It is not anticipated that results of study of your neurofibroma tissue will influence clinical management, and therefore you will not be informed of research results on this tissue. All research results will be kept confidential. You can withdraw your specimen from the tissue repository at any time.

RISKS AND DISCOMFORTS:

8. Clinical Assessment: The clinical assessments will be the standard ones performed in our Neurofibromatosis Clinic, with the addition of measurement of any visible plexiform neurofibroma. This assessment may cause some embarrassment, anxiety, and inconvenience. We will make every effort to insure that the clinic visits occur in an efficient and dignified manner, and will make every effort to explain what is being done and what is found. The clinic visits will be billed as standard clinical assessments. We will obtain prior approval from your child's insurance company and to explain that clinical follow-up of plexiform neurofibromas is appropriate clinical care.

9. Photography of Plexiform Neurofibromas: The photographs will be taken only of the region of your child's body affected by the plexiform neurofibroma. These photographs will be kept in a confidential file and will not contain your child's name. In some cases they may be used for teaching purposes or in scientific or medical publications related to this work, however.

10. Clinical Database: The clinical database is kept on a computer in a password-protected file. There is a potential risk of your clinical information being read by unauthorized persons, although the use of a password system should minimize this risk. To preserve your child's privacy, any data sent to the central database will be sent without any personal identifying information. Your child will be identified in the central database only by a code number, and our clinic will be the only place where the code number can be linked to your child's name.

11. Blood Sampling: The blood sampling procedure involves insertion of a needle into a vein in the arm and withdrawing 5 – 10 cc of blood (1 – 2 teaspoons). We expect to take only 5 cc (1 teaspoon) from children under five years of age and no more than 10 cc (2 teaspoons) from children over five years of age or from adults. There is discomfort associated with blood drawing, and very slight risk of infection due to insertion of the needle. There is also risk of redness, bruising, and swelling at the site from which the blood is removed. Blood will be drawn in the Children's Hospital phlebotomy (blood drawing) center, and every effort will be made to minimize the pain and to obtain the blood using sterile procedures.

12. Genetic Studies: Although there is no immediate plan to perform genetic studies from the blood samples obtained, genetic material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that DNA samples will be stored indefinitely in this repository. The sample will be identified by a code number that can be traced to your child only by contact with our clinic. Genetic testing may eventually reveal the neurofibromatosis gene mutation that is responsible for NF1 in your child. Although genetic testing can, in some cases, result in discrimination for health or life insurance or employment, we believe that these risks are minimal since it is already known that your child has neurofibromatosis. It may also be possible to examine other genes that may influence the growth of neurofibromas in persons with NF1. Some of these may be genes that themselves can have implications for health. You will be given an opportunity to indicate whether you wish to know about any results that may be obtained, and whether you would like us to share these results with your child's health provider. We will keep all results confidential, however, and not disclose them to any other individual without your permission.

13. Tumor Studies: Tumor material will be obtained only if surgery is indicated for clinical reasons, and only after the pathologist and surgeon have determined that any material necessary for clinical care has been obtained. We will not ask that additional tumor material be obtained solely for research purposes, and will confine any tissue saved for research purposes to any excess tumor available after clinical studies are completed. Although there is no immediate plan to perform studies from any tumor samples obtained, tumor material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that the tissue samples will be stored indefinitely in the repository. The sample will be identified by a code number that can be traced to your child only by contact with our clinic. No results will be placed in your medical record or disclosed to anyone without your permission.

14. MRI: Magnetic resonance imaging (MRI) is a standard procedure used for imaging plexiform neurofibromas. There are no known or foreseeable risks

associated with exposures to MRI provided no metal implanted prostheses (*e.g.,* vascular clamps or pacemakers; braces are not a problem). All potential subjects will be screened for the presence of such prior to the examination. Some participants in the study may require sedation or anesthesia to perform MRI. Consent for this will be obtained prior to the study. It must be recognized that there are risks associated with sedation and anesthesia, including the risk of death in rare instances. The MRI scans and sedation/anesthesia costs will be billed to insurance.

POTENTIAL BENEFITS:

This study is being performed in conjunction with routine clinical care. It is standard to see individuals with neurofibromatosis in clinic at least once per year and more often if there is a problem such as plexiform neurofibroma. MRI imaging of plexiform neurofibromas is also done as part of standard clinical care. It is possible that, in the course of this study, growth of a plexiform neurofibroma will be discovered that requires further treatment, most likely surgical. In that case, referral to a surgeon who is familiar with the management of plexiform neurofibromas will be made. The MRI data in this study will be analyzed by a special approach called "volumetric MRI," in addition to being read in a standard manner by a radiologist. It is expected that the volumetric MRI approach will provide more precise measurement of the size of plexiform neurofibromas, and therefore will give more complete and objective information on which to base any possible future treatment decisions. Volumetric MRI is currently not available on a routine clinical basis.

ALTERNATIVES:

If you chose not to have your child participate in this study, it will not influence your child's care or management in the Neurofibromatosis Program. It may be deemed necessary for your child to have routine clinical assessments for a plexiform neurofibroma, which may include MRI scanning, but this will be done outside the context of the research study if you choose. This means that the data will not be shared with the central data facility and that DNA and potential tumor samples will not be obtained. Otherwise your child's care will be the same.

VOLUNTEER REGISTRY DATA BASE REQUIREMENTS:

This study is supported by the U.S. Army. It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your child's name, address, Social Security number, study name, and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can

exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risk and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

MEDICAL CARE FOR RESEARCH RELATED INJURY:

Should your child be injured as a direct result of participating in this research project, your child will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your child's legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

REVIEW OF RESEARCH RECORDS:

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

CONSENT:

I have fully explained to _____ the nature and
Parent/guardian
purpose of the above-described procedures and the risks involved in their performance. I have answered and will answer all questions to the best of my ability. I will inform the participant of any changes in the procedures or the risks and benefits if any should occur during or after the course of the study. I have given a copy of the consent form to the family.

_____ _____
Date Investigator's and/or Associate's Signature

CONSENT:

I have been satisfactorily informed of the above-described procedure and with its possible risks and benefits. I give permission for my child's participation in this study. I know that Dr. Korf or his associates may be reached at (617) 355-6394 and will be available to answer any questions that I may have. If I have questions regarding my child's rights as a research subject or questions regarding compensation in the event of a research related injury, I may request to speak with a member of the Hospital Consent Committee by calling (617) 355-7052. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect my child's care. I have been given a copy of this form.

I understand that there is a possibility that the blood, tissue, body fluid, or sample(s) of neurofibroma tissue that I am providing under this study may also be used in other research studies and could potentially have some commercial applicability.

_____ _____

Date Signature of Parent/Guardian

Name of Parent/Guardian _____

Address _____

_____

_____ _____

Date Witness to Signatures

Name of Witness _____

Address of Witness _____

_____

6/14/99

Disclosure of Information Obtained from Genetic Studies

Please indicate whether you wish to be informed of any results of genetic studies that may be relevant to your health or to genetic counseling of you or your family:

I wish to be informed of the results of any genetic tests performed on my/my child's blood or tumor tissue that may have implications for health care or genetic counseling.

I do not wish to be informed.

Please indicate the name and address of any health provider to whom you would like any results sent.

Name: _____

Address: _____

City: _____

State: _____ Zip: _____

6/14/99

Sample Donation Form

Natural History of Plexiform Neurofibromas in NF1

I voluntarily and freely donate any and all blood, tissues, body fluid, product, or sample(s) of neurofibromas to Children's Hospital and hereby relinquish all right, title, and interest to said items.

_____ _____

Date Signature of Parent

Name of Participant _____

Address of Participant _____

_____

_____ _____

Date Witness to Signatures

Name of Witness _____

Address of Witness _____

_____

6/14/99

Appendix C

VOLUNTEER REGISTRY DATA SHEET

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397

2. Principal and Routine Purposes: To document participation in research conducted or sponsored by the U.S. Army Medical Research and Materiel Command. Personal information will be used for identification and location of participants.

3. Mandatory or Voluntary Disclosure: The furnishing of the SSN is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide information may preclude your participation in the research study.

PART A - INVESTIGATOR INFORMATION

(To Be Completed By Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

1. Study Number:_____ 2. Protocol Title:

3. Contractor (Laboratory / Institute Conducting Study):

4. Study Period: From: ____/____/____ To: ____/____/____
DD MM YY DD MM YY

5. Principal / Other Investigator(s) Names(s): 6. Location / Laboratory

1. _____ _____/_____
2. _____ _____/_____
3. _____ _____/_____

PART B - VOLUNTEER INFORMATION

(To Be Completed By Volunteer)

PLEASE PRINT, USING INK OR BALLPOINT PEN

7. SSN: _____/_____/_____ 8. Name: _____

9. Sex: M____F____ 10. Date of Birth: _____/_____/_____ 11: *MOS/Job Series_____ 12: Rank/Grade _____

13. Permanent Home Address (Home of Record) or Study Location:

_____ _____
(Street) (P.O. Box / Apartment Number)

_____ _____ _____ _____
(City) (Country) (State) (Zip Code)

Permanent Home Phone Number: _____

14. * Local Address (If Different From Permanent Address):

_____ _____
(Street) (P.O. Box / Apartment Number)

_____ _____ _____ _____
(City) (Country) (State) (Zip Code)

Local Phone Number: _____

15. * Military Unit: _____ Zip Code: _____

Organization: _____ Post: _____ Duty Phone Number: _____

USAMRDC Form 60-R Revised 1 Apr 88 (Supersedes previous editions)

PART C - ADDITIONAL INFORMATION

(To Be Completed By Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

16. **Location of Study:** _____

17. **Is Study Completed: Y:** _____ **N:** _____

Did volunteer finish participation: Y: _____ **N:** ____ **If YES, date finished** _____/_____/_____
DD MM YY

If NO, date withdrawn: _____/_____/_____ **Reason Withdrawn:**
DD MM YY

18. **Did any Serious or Unexpected Adverse Incident or Reaction Occur: Y:** _____ **N:** _____ **If YES, Explain:**

19. *** Volunteer Follow-up:** _____

Purpose: _____

Date: _____/_____/_____ **Was contact made: Y:** _____ **N:** _____ **If no action taken, explain:**

20. *** Hard Copy Records Retired: Place:** _____ **File NR:** _____

21. *** Product Information:**

Product: _____

Manufacturer: _____

Lot NR: _____ **Expiration Date:** _____

NDA NR: _____ **IND/IDE NR:** _____

- **Indicates that item may be left blank if information is unavailable or does not apply. Entries must be made for all other items.**

When completed, a copy of this form should be sent to the address below:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
Fort Detrick, MD 21702-5012

Appendix D

Patient Registration Form

Natural History of Plexiform Neurofibromas in NF1

Fax this form to Mary Sanford at Children's Hospital, **(617) 355-7588**. Please call (617) 355-3479 if there are problems with fax transmission.

Institution _____

Physician _____

Fax _____

Patient Information

Database ID # _____ Please refer to the instructions in the Procedures and Policies Manual

Age _____

Sex M F

Plexiform Site (Check One)
Refer to Manual for Definitions

- ☐ Head and Neck
- ☐ Trunk and Limbs (externally visible)
- ☐ Trunk and Limbs (internal)

Prior Surgery Y N *If yes, DATE* _____

Diagnostic Criteria

- ☐ Six or more *café-au lait*-macules
- ☐ Freckling in the axillary or inguinal region
- ☐ Neurofibromas
- ☐ Lisch nodules
- ☐ Optic glioma
- ☐ Tibial or orbital dysplasia
- ☐ Family History

To be completed by Children's Hospital only:

Natural History of Plexiform Neurofibromas in NF1 ID#: ☐

- ☐ Yes, We will include this patient in the study of Natural History of Plexiform Neurofibromas in NF1. Please refer to the assigned patient ID# in the future.
- ☐ No, Unfortunately this patient does not meet the needs of this study.

Date Reviewed:

Approved by: _____

Appendix E

Patient Withdrawal Form

Natural History of Plexiform Neurofibromas in NF1

Fax this form to Mary Sanford at Children's Hospital, **(617) 355-7588**. Please call (617) 355-3479 if there are problems with fax transmission.

Date _____

Institution _____

NF Patient ID# _____

Reasons for Withdrawal:

_____ _____

Physician Signature Date

Appendix F

Adverse Events Form

Natural History of Plexiform Neurofibromas in NF1

Fax this form to Mary Sanford at Children's Hospital, **(617) 355-7588**. Please call (617) 355-3479 if there are problems with fax transmission.

Date _____

Institution _____

NF Patient ID# _____

Date of Visit _____

Description of Adverse Events:

_____ _____

Physician Signature Date

Appendix G

NNFF International Database - 1999 Update

The database now contains clinical information on approximately 4000 individuals with NF, collected at over 30 centers throughout the world. Any NF clinic is welcome to contribute to, and obtain data from, this resource.

We have updated the database to allow data entry via the Internet and/or via scannable paper forms, although the existing DOS-based system will still remain an option. We have also redesigned the database to consist of 7 demographic questions, 25 core NF questions, and optional modules designed to record detailed information for each of the following specialities: dermatology, ophthalmology, neurology, psychology/cognitive development, endocrinology, dysmorphology, and orthopaedics.

Scannable Forms

The scannable paper forms are enclosed. As you can see, they are mostly multiple choice, and they have an area to record notes, pedigrees or diagrams. When they are scanned into the computer, the multiple-choice questions are recorded in the database and the notes and diagrams are stored as a graphic image. Optical character recognition software allows hand-written numbers, such as date of visit, and head circumference, to be stored in the database.

To date, the scannable forms are available only for the demographic and core questions. We will design and implement the optional modules if there is a demand for this system.

Paper forms were chosen because they enable data entry to occur during a clinic visit and may become part of the permanent clinic record. Scanning data into the computer avoids the time required to manually enter data as well as avoiding most data entry errors. Another major advantage of the paper forms is that they may be translated into any language. You may use the forms immediately. Please photocopy as many as you need for your clinic.

Web Data Entry

Our new web version of the database contains the same demographic questions, core questions and optional modules as described above. This data entry system is designed to be as rapid as possible via the Internet. Clinics will be able to add and edit data for their own patients and will also have read-only access to clinical data for all other patients on the database. A sophisticated search procedure will allow authorised clinicians to perform database searches.

Information on accessing the web version of these forms appears on a separate sheet along with the web address, your user name and password. The best way to get to know this program is to try it out but we are available for questions:

Email: birch@interchg.ubc.ca,
Phone: 604-822-5348
Fax: 604-822-2749
Mail: U.B.C. Dept. of Medical Genetics,
222-6174 University Blvd.,
Vancouver, B.C. V6T 1Z3
Canada

Using the Scannable Forms

Enclosed are copies of the Demographic Form and Core Questions. These are the questions that are obligatory in the revised database.

If you would like to contribute data using these forms you may do so immediately. Please note that the forms are specifically coded for your centre. Don't use anyone else's forms!

The forms are "read" by a computer. This means that there are certain rules to follow:

1. For the multiple-choice options, please completely fill circles (for each choice) with a dark-coloured pen or pencil. Several of the questions (e.g. Ethnic Origin, on the Demographic Form) can accept more than one option per question. In these cases, complete as many as are necessary.

2. For the scannable data (database numbers, dates, height and head circumference), please print clearly, one number to each box. Avoid touching the box lines with your pen.

You may transmit the forms to us by fax, or you may mail them to me in batches. Please make sure that the forms for each patient stay together!

For more information, please do not hesitate to contact Patricia Birch, Database Coordinator:

Email: birch@interchg.ubc.ca,
Phone: 604-822-5348
Fax: 604-822-2749
Mail: U.B.C. Dept. of Medical Genetics,
222-6174 University Blvd.,
Vancouver, B.C. V6T 1Z3
Canada

Assigning a Database Number

If you have used the database before...
you will know that the database number consists of a three digit *site number* (which is pre-filled in the scannable forms); a four digit *family number*; and a three digit *individual number*. As before, you need to assign the family and individual numbers for each patient. If you have entered data via the old system, please continue with whatever method you now use to assign these numbers.

If you are new to the database,
you need to know that the database number consists of a three digit *site number*; a four digit *family number*; and a three digit *individual number*. You need to assign the family and individual numbers for each patient

Assigning a site number
The site number is assigned by us. Your site number is attached to your user name and is automatically filled in when you enter data by the web. If you are using the paper forms, the site number has been pre-filled for you.

Assigning family numbers
Start with family number "0001," and number each new family sequentially: "0002," "0003,"....

Assigning individual numbers
To assign an individual number, you may devise your own method, or you may choose one of two methods described below:

Method 1: Some centres number the proband "001" and number other family members sequentially: "002," "003,"...

Method 2: Other centres number the proband "500," and his or her generation sequentially: "501," "502," "503." The proband's children's generation are numbered starting with "600," "601," etc., and the proband's parent's generation are numbered starting with "400," "401," etc.

Names are not recorded on the database. This adds a level of confidentiality, but puts the onus on data contributors to keep track of the data they have entered. **Keep a record in your own clinic of the family and individual numbers that you assign to patients. Without this, it will be very difficult to link the database number to your own patients!**

Appendix H

Draft

Natural History of Plexiform Neurofibromas in NF1
NNFF International Database

NF Database Number ☐☐☐ ☐☐☐☐ ☐☐☐

Plexiform Study Number ☐☐☐

Date of Exam
☐☐ / ☐☐ / ☐☐
year / month / day

Sex
O Male
O Female

Year of Birth
☐☐☐☐

I. General Information

On this visit, indicate if the patient has had:

O MRI
O Photograph Taken
O Blood Sample Taken
O Tissue Specimen Taken

Clinical evidence of growth of plexiform O Yes O No O Uncertain

Criteria for Tanner Staging - See Procedure Manual

MALE
Tanner Stage O One O Two O Three O Four O Five

FEMALE
Tanner Stage - Pubic O One O Two O Three O Four O Five
Tanner Stage - Breasts O One. O Two O Three O Four O Five
Oral Contraceptives O Yes O No O Uncertain O Not applicable
Pregnant O Yes O No O Uncertain O Not applicable

II. Plexiform Study Group

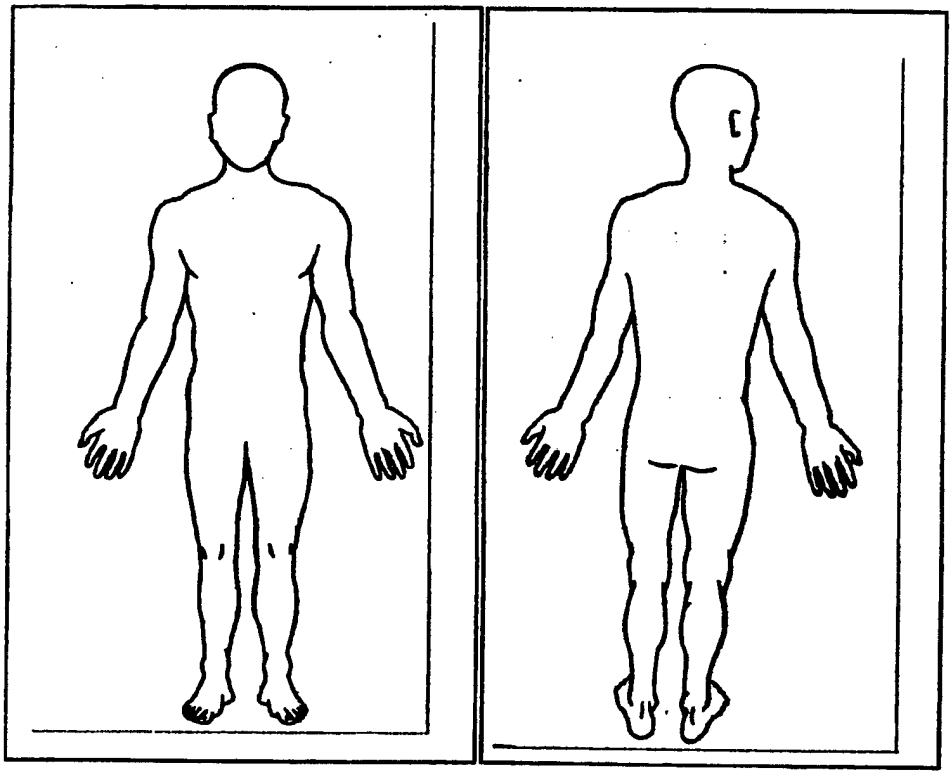
O Head and Neck
O Trunk and Limbs (Externally Visible)
O Trunk and Limbs (Internal)

III. Location and Size

A. Please choose the area which best describes the location of the plexiform.

O Head	O Left Arm	O Right Arm	O Dorsal
O Neck	O Left Leg	O Right Leg	O Ventral

B. Please mark approximate location on the diagram below.



C. In the box below, you may draw the tumor, add multiple measurements, noting anatomical landmarks to ensure measurement consistency over time.

D. Externally Measureable O Yes O No

Diameter One | | | mm

Diameter Two | | | mm

IV. Appearance, Signs and Symptoms

A. Externally Visible O Yes O No

If YES, please answer the following questions. If NO go to Section V.

O Cutaneous Hyperpigmentation
O Cutaneous Hypertrophy
O Increased Skin Vascular Markings
O Decreased Skin Vascular Markings
O Palpable Mass
O Hair Growth from Tumor Site

B. Facial Involvement O Yes O No

If YES, please answer the following questions. If NO go to Section IV.C.

Eyes

Upper Lid O Left O Right
Lower Lid O Left O Right
Proptosis O Left O Right
Enophthalmos O Left O Right
Glaucoma O Left O Right

Face

O Forehead
O Cheek
O Nose
O Upper Lip
O Lower Lip
O Jaw
O Pre-auricular
O Pinna
O Post-auricular
O Tongue
O Upper Aveolar Ridge
O Lower Aveolar Ridge

C. Limb Hypertrophy O Yes O No

If YES, please answer the following questions. If NO go to Section V.

Upper Arm	O Left	O Right
Forearm	O Left	O Right
Hand	O Left	O Right
Thigh	O Left	O Right
Lower Leg	O Left	O Right
Foot	O Left	O Right

V. Functional Impairment O Yes O No

If YES, please answer the following questions. If NO go to Section VI.

O Airway Obstruction
O Pain
O Weakness
O Sensory Change
O Disfigurement

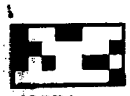
VI. Questions to ask Patient

A. Did you notice any of the following in the area around your neurofibroma?

O Weakness
O Numbness
O Changes in sensation such as tingling
O Pain
O Itching
O Bleeding or Oozing

B. Do you think the neurofibroma is growing? O Yes O No O Uncertain

VII. Additional Comments



49574

NNFF International Database
Demographic Questions

NF Database Number ☐☐☐ ☐☐☐☐ ☐☐☐

Local ID Number ☐☐☐☐☐☐☐☐☐☐☐☐

1 Sex

- O Male
- O Female

2 Date of Birth

☐☐☐☐ / ☐☐ / ☐☐

year / month / day

3 Date of death

☐☐☐☐ / ☐☐ / ☐☐

year / month / day

4 Type of NF

- O NF 1
- O Possible NF1
- O Segmental NF1
- O Other Type (include Watson Syndrome)
- O NF2
- O Unknown

5 Inheritance

- O New mutation
- O Mother affected
- O Father affected
- O Both parents affected
- O Unknown

49574

6 Ethnic Origin

- O Asian - Japanese
- O Asian - Chinese
- O Asian - Indian Subcontinent
- O Asian - Other
- O Asian - Unknown
- O Black
- O Latin American
- O Native American
- O White
- O Other
- O Unknown

7 Date of Exam

				/			/		

year / month / day

50590

NNFF International Database
Core Questions

NF Database Number ☐☐☐ ☐☐☐☐ ☐☐☐

Local ID Number ☐☐☐☐☐☐☐☐☐☐☐

1 Date of Exam

☐☐☐☐ / ☐☐ / ☐☐

year / month / day

2 Height/length (leave blank if unknown)

☐☐☐.☐ **cm**

☐ ft ☐☐.☐ in

3 Head Circumference

☐☐.☐ **cm**

☐☐.☐ **in**

4 Number of cafe au lait > 1.5 cm (> 0.5 cm pre-puberty)

- O None
- O 1
- O 2
- O 3
- O 4
- O 5
- O 6 or more
- O Present, number unknown
- O Unknown

5 Intertriginous Freckling

- O Absent
- O Present
- O Unknown

50590

6 Subcutaneous neurofibromas

- O None
- O 1
- O 2
- O 3-9
- O 10-50
- O >50
- O Unknown

7 Cutaneous neurofibromas (including pendulous)

- O None
- O 1
- O 2
- O 3-9
- O 10-50
- O >50
- O Unknown

8 Plexiform neurofibroma - Location (check as many as apply)

- O None
- O Orbit
- O Face
- O Head/neck
- O Trunk - dorsal
- O Trunk - ventral
- O Arm
- O Leg
- O Unknown

9 Paraspinal neurofibromas

- O Absent by scan
- O Absent clinically
- O Present
- O Unknown

10 Xanthogranulomas

- O Absent
- O Present
- O Unknown

11 Lisch nodules

- O Absent
- O Present on slit lamp example
- O Possible
- O Unknown

50590

12 Proptosis

- O Absent
- O Unilateral
- O Bilateral
- O Present, laterality unknown
- O Unknown

13 Optic glioma

- O Absent by scan
- O Absent clinically
- O Present - asymptomatic
- O Present - symptomatic
- O Unknown

14 Seizures type

- O None
- O Febrile only
- O Hypsarrhythmia
- O Generalized
- O Partial
- O Multiple types
- O Present - type unknown
- O Other
- O Unknown

15 Hydrocephalus

- O Absent clinically
- O Absent by scan
- O Aqueductal stenosis
- O Other non-communicating
- O Communicating
- O Present - type unknown
- O Unknown

16 Intellectual Development

- O Normal
- O Mildly Delayed
- O Significantly Delayed
- O Unknown

50590

17 Learning Problems

- O None
- O Specific learning problems present
- O Unknown

18 Hypertension

- O Absent
- O Present
- O Unknown

19 Congenital heart disease

- O Absent clinically
- O Absent by special testing
- O Aortic stenosis
- O ASD
- O Patent ductus arteriosis
- O Pulmonic stenosis
- O Tetralogy of Fallot
- O VSD
- O Other type of CHD
- O Multiple types of CHD
- O Possible CHD
- O Unknown

20 Vascular anomalies

- O Absent clinically
- O Renal artery stenosis
- O Arterial stenosis (non-renal)
- O Moya moya
- O Other
- O Unknown

21 Age puberty began

- O <10
- O 10-15
- O >15
- O Not Applicable
- O Unknown

50590

22 Dysmorphic features

- O No
- O Yes
- O Possible
- O Unknown

23 Congenitally bowed tibia or pseudoarthrosis

- O Absent clinically
- O Absent radiographically
- O Present
- O Unknown

24 Dysplastic vertebrae

- O Absent clinically
- O Absent radiographically
- O Present
- O Unknown

25 Scoliosis

- O Absent clinically
- O Absent radiographically
- O Present
- O Unknown

26 Dysplastic sphenoid wing

- O Absent clinically
- O Absent radiographically
- O Present - bilateral
- O Present - unilateral
- O Present - laterality unknown
- O Unknown

50590

27 Neoplasm type

- O None
- O Carcinoma
- O Ependymona
- O Glioma
- O Leukemia
- O Lymphoma
- O Malignant peripheral nerve sheath tumour
- O Meningioangiomatosis
- O Meningioma
- O Pheochromocytoma
- O Sarcoma
- O Schwannoma
- O Malignancy present, type unknown
- O Other

28 Comments

Appendix I

Tanner Stages

Male

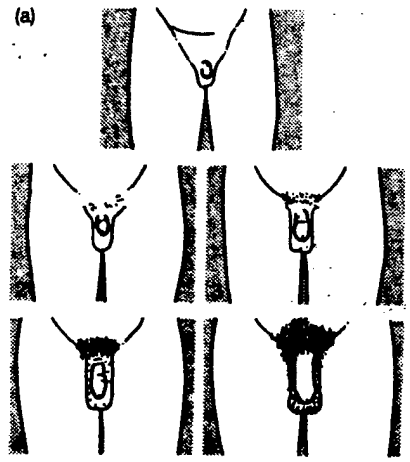


Fig. 10.2(a) Male genital development (G-1–G-5) and public hair (PH-1 to PH–5). Tanner stages. (From Tanner (1975), by permission.)

Female

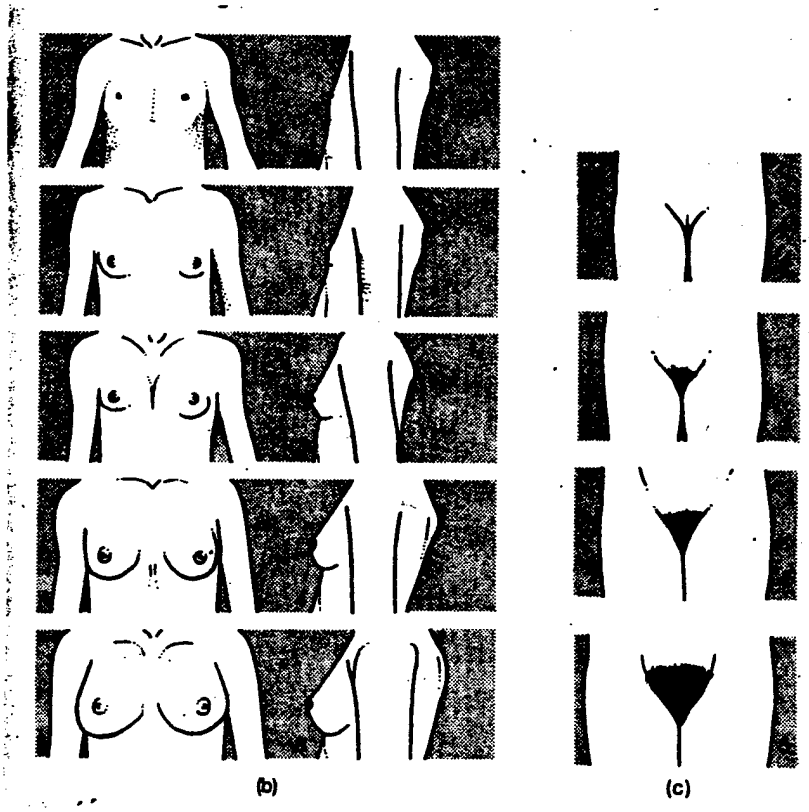


Fig. 10.2(b) Female breast development (B-1–B-5) and (c) pubic hair (PH–2 to PH–5). Tanner stages. (From Tanner (1975), by permission.)

Note: These illustrations were adapted from the Handbook of Normal Physical Measurements.

Appendix J

MRI Reimbursement Form

Natural History of Plexiform Neurofibromas in NF1

MRIs will be reimbursed at the your institution's *Research Rate*. Please check will your radiology or research departments for your institutions rate.

Date _____

Institution _____

MRI Research Rate _____

NF Patient ID# _____

Date of Visit _____ ***Date of Last MRI*** _____

Does the patient have insurance? **YES** **NO**

If YES, reason for denial:

_____ _____
Physician Signature Date

To be completed by Children's Hospital only:

Date:

☐ **We will reimburse you an amount of** $_____ **for the MRI.**

☐ **MRI is not necessary at this time.**

Appendix K

Form Completed By:_____ Date: (Mo/D/Yr) __ __/ __ __/ __ __

NF1 WorldCare Site Survey and Qualification Form

Information you enter here will be used to qualify your MRI site as a Patient Collection Center for participation in the NF2 Natural History Study. All information will be kept confidential.

Section 1 – MRI Site Contact Information

1. Person responsible for NF1 Natural History Study at this site:

Name: _____

Position: _____

Email: _____

Phone #: _____

Fax: _____

Address: _____

_____

_____

2. Technical contact (scanner/network):

Name: _____

Position: _____

Email: _____

Phone: _____

Fax: _____

Pager: _____

Section 2 – MRI Scanner Information

3. Name of MRI site: _____

4. Manufacturer of MRI: _____

5. Model Number of MRI: _____

6. Year MRI was Purchased: _____

Form Completed By:_____ Date: (Mo/D/Yr) __ __/ __ __/ __ __

Section 3 – DICOM 3.0 Export Information

7. **Can Your MRI Export it's Image Data in a DICOM 3.0 Format?** Yes / No

If YES go to A and skip section 4. If No go to section 4.

A. Does your machine act as a DICOM 3.0 Server? Yes / No

B. Can your MRI DICOM 3.0 Server push data through an Intranet via a dial up modem or an ISDN line without being hindered by existing firewalls?

Yes / No

C. Does your MRI machine push its DICOM 3.0 format to another machine that acts as a DICOM 3.0 Server?

Yes / No

D. Can that DICOM 3.0 Server push data through an Intranet via a dial up modem or an ISDN line without being hindered by existing firewalls?

Yes / No

E. If your system is blocked by existing firewalls, are you able to output the DICOM 3.0 data to some sort of media?

Yes / No

F. If yes what type of media? _____

G. What is the manufacturer of the media? Please list model numbers:

_____

H. What is the manufacturer of the drive? Please list model numbers:

_____

I. Is there a host machine hooked to the drive? Please describe:

_____

J. Is there a Pioneer Optical Drive hooked to your system?

Yes / No

K. If no, can a Pioneer Optical Drive be added?

Yes / No

Section 4 – Alternative File Format Information

8. **If your MRI Raw Data is not exported in DICOM 3.0 format, please list the specifications of the file format.**

_____

_____

A. Does your MRI output to a server that understands the format?

Yes / No

Form Completed By:_____ Date: (Mo/D/Yr) __ __/ __ __/ __ __

B. Can that server push data through an Intranet via a dial up modem or an ISDN line without being hindered by existing firewalls?

Yes / No

C. If your system is blocked by existing firewalls, are you able to output the data to some sort of media?

Yes / No

D. If yes what type of media? _____

E. What is the manufacturer of the media? Please list model numbers:

_____

F. What is the manufacturer of the drive? Please list model numbers:

_____

G. Is there a host machine hooked to the drive? Please describe:

_____

H. Is there a Pioneer Optical Drive hooked to your system?

Yes / No

I. If no, can a Pioneer Optical Drive be added?

Yes / No

Section 5 – Additional Network and Software Information

9. Communications information for your scanner:

Network Interface Card:

IP: _____

Subnet mask: _____

Gateway: _____

DNS: _____

10. DICOM 3.0 sources

First source:

Modality type: _____ **MRI** _____

Manufacturer/model: _____

Software Name, Rev #: _____

Second source (if any):

Modality type: _____

Manufacturer/model: _____

Software Name, Rev #: _____

NF1 MRI Site Test Data Qualification Form

This section to be completed by the MRI site:

1. **Name and title of person performing test data transfer:** _____
2. **Date of test data transfer:** _____
3. **What modality is the test data set?** **OD / FTP / Other:** _____
4. **If optical disk (OD), what is the manufacturer and model number?**
   _____
5. **Briefly describe the contents of the test data set:** _____

_____

_____

This section to be completed by the WorldCare Measurement Center:

1. **Can the test data set received be converted to DICOM 3.0?** **Yes / No**
2. **Is the test data readable and the quality of all images acceptable for image analysis?** **Yes / No**
3. **If NO, briefly describe the problems with the test data set:** _____

_____

_____

The undersigned WorldCare Measurement Center representative acknowledges that the test data set is acceptable in accordance with NF2 WCMC Standard Operating Procedures.

_____

Signature **Title** **Date**

Appendix L

NF Database ID#_____ Date of Scan_____
NF Study#_____

NF1 MRI DATA COLLECTION FORM

To:	**Mary Sanford**	From:	
Fax:	(617) 525 - 5757	Site:	
Phone:	(617) 525 - 5758	Site Phone #:	
Re:	Patient Collection Information	Site Fax #:	

This form must be completed by investigative sites and faxed to Boston Children's Hospital ***with Acquisition Protocol*** *within one working day after patient images have been acquired:*

MRI Acquisition Protocol ***(Please choose one.)***

☐ **Head and Neck**

☐ **Trunk and Extremities**

☐ **Spine**

Data Transfer Information

Date to transfer images: _____/_____/_____

Data Transmission Modality: _____*(optical disk or FTP)*

Shipping Number: _____*(if applicable)*

Disk Label *(if optical disk):* _____

SEND THIS FORM WITH APPROPRIATE ACQUISITION PROTOCOL FORM *AND* KEEP A COPY FOR YOUR RECORDS

Received by Children's Hospital _____

Appendix M

NF Database ID#_____ Date of Scan_____
NF Study#_____

NF1 ACQUISITION PROTOCOL

MRI PROTOCOL-HEAD/NECK

NOTE: ALL SERIES WITH THE EXCEPTION OF # 2 AND #3 SHOULD BE PERFORMED PER A NORMAL CLINICAL SCAN AS SPECIFIED BY THE RADIOLOGIST. THESE ADDITIONAL SERIES #2 AND #3 MAY OR MAY NOT BE PART OF THE NORMAL CLINICAL SCAN SEQUENCE, HOWEVER THESE SERIES ARE REQUIRED FOR THE NF1 STUDY PROTOCOL AND MUST BE PERFORMED WITHIN PROTOCOL SPECIFICATIONS AS INDICATED BELOW.

1. SAGITTAL T1 — PER NORMAL CLINICAL SCAN

2. AXIAL FSEIR

	Protocol Specifications	Actual Specifications	Reason For Change
▪ ECHO TRAIN LENGTH: 8			
▪ TR	6000	_____	_____
▪ TE	34	_____	_____
▪ TI	150	_____	_____
▪ SLICE THICKNESS	4 MM	_____	_____
▪ SKIP	0	_____	_____
▪ MATRIX	256 X 256	_____	_____
▪ FOV	22 CM	_____	_____
▪ NEX	1	_____	_____
▪ FREQUENCY DIRECTION	A→P	_____	_____
▪ OPTIONS: TAILORED RF, FC, 0.75 FOV			

3. CORONAL FSEIR

▪ ECHO TRAIN LENGTH: 8			
▪ TR	6000	_____	_____
▪ TE	34	_____	_____
▪ TI	150	_____	_____
▪ SLICE THICKNESS	5 MM	_____	_____
▪ SKIP	0 MM	_____	_____
▪ MATRIX	256 X 192	_____	_____
▪ FOV	22 CM	_____	_____
▪ NEX	1	_____	_____
▪ FREQUENCY DIRECTION	S→I	_____	_____
▪ OPTIONS: TAILORED RF, PC			

4. AXIAL T1- PRE CONTRAST — PER NORMAL CLINICAL SCAN

5. AXIAL T1- POST CONTRAST — PER NORMAL CLINICAL SCAN

MRI Technician_____ Received by Children's Hospital _____

NF Database ID#_____ Date of Scan_____
NF Study#_____

NF1 ACQUISITION PROTOCOL

MRI PROTOCOL-TRUNK/EXTREMITIES

NOTE: ALL SERIES WITH THE EXCEPTION OF # 1 AND #2 SHOULD BE PERFORMED PER A NORMAL CLINICAL SCAN AS SPECIFIED BY THE RADIOLOGIST. THESE ADDITIONAL SERIES #1 AND #2 MAY OR MAY NOT BE PART OF THE NORMAL CLINICAL SCAN SEQUENCE, HOWEVER THESE SERIES ARE REQUIRED FOR THE NF1 STUDY PROTOCOL AND MUST BE PERFORMED WITHIN PROTOCOL SPECIFICATIONS AS INDICATED BELOW.

1. AXIAL PLANE-STIR	Protocol Specifications	Actual Specifications	Reason For Change
▪ COIL: BODY			
▪ SEQUENCE: FAST SPIN ECHO (TURBO) FSEIR			
▪ ECHO TRAIN LENGTH: 8			
▪ TR	6000	_____	_____
▪ TE	15	_____	_____
▪ TI	150	_____	_____
▪ SLICE THICKNESS	10 MM	_____	_____
▪ SKIP	0	_____	_____
▪ MATRIX	512x160	_____	_____
▪ FOV	40 X 30	_____	_____
▪ NUMBER OF EXCITATIONS/SEQUENCE	0.5	_____	_____
▪ NUMBER OF ACQUISTIONS	1	_____	_____
▪ SATURATION	NONE	_____	_____

2. CORONAL PLANE - STIR			
▪ COIL: BODY			
▪ SEQUENCE: FAST SPIN ECHO (TURBO) FSEIR			
▪ ECHO TRAIN LENGTH: 12			
▪ TR	3400	_____	_____
▪ TE	15	_____	_____
▪ TI	150	_____	_____
▪ SLICE THICKNESS	5 MM	_____	_____
▪ SKIP	0	_____	_____
▪ MATRIX	512 X 160	_____	_____
▪ FOV	48 X 48	_____	_____
▪ NUMBER OF EXCITATIONS/SEQUENCE	1	_____	_____
▪ NUMBER OF ACQUISTIONS	1	_____	_____
▪ SATURATION	NONE	_____	_____

MRI Technician_____ Received by Children's Hospital _____

NF Database ID#_____ Date of Scan_____
NF Study#_____

NF1 ACQUISITION PROTOCOL

MRI PROTOCOL- SPINE

NOTE: ALL SERIES WITH THE EXCEPTION OF # 4 AND #5 SHOULD BE PERFORMED PER A NORMAL CLINICAL SCAN AS SPECIFIED BY THE RADIOLOGIST. THESE ADDITIONAL SERIES #4 AND #5 MAY OR MAY NOT BE PART OF THE NORMAL CLINICAL SCAN SEQUENCE, HOWEVER THESE SERIES ARE REQUIRED FOR THE NF1 STUDY PROTOCOL AND MUST BE PERFORMED WITHIN PROTOCOL SPECIFICATIONS AS INDICATED BELOW.

1. SAGITTAL T1 LOCALIZER—SPINE COIL — PER NORMAL CLINICAL SCAN
2. SAGITTAL T1 — PER NORMAL CLINICAL SCAN
3. SAGITTAL FSEIR — PER NORMAL CLINICAL SCAN

4. AXIAL FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
▪ ECHO TRAIN LENGTH: 8			
▪ TR	6000	_____	_____
▪ TE	34	_____	_____
▪ TI	150	_____	_____
▪ SLICE THICKNESS	5 MM	_____	_____
▪ SKIP	0	_____	_____
▪ MATRIX	256 X 256	_____	_____
▪ FOV	22 CM	_____	_____
▪ NEX	1	_____	_____
▪ FREQUENCY DIRECTION	R→L	_____	_____
▪ OPTIONS: TAILORED RF, FC, PC, 0.75 FOV			

5. CORONAL FSEIR			
▪ ECHO TRAIN LENGTH: 8			
▪ TR	6000	_____	_____
▪ TE	34	_____	_____
▪ TI	150	_____	_____
▪ SLICE THICKNESS	5 MM	_____	_____
▪ SKIP	1 MM	_____	_____
▪ MATRIX	256 X 256	_____	_____
▪ FOV	22 CM	_____	_____
▪ NEX	1	_____	_____
▪ FREQUENCY DIRECTION	S→I	_____	_____
▪ OPTIONS: TAILORED RF, FC, PC			

6. AXIAL T1 — PER NORMAL CLINICAL SCAN
7. AXIAL T1- POST CONTRAST — PER NORMAL CLINICAL SCAN

Appendix N

NF Patient ID#_____ **Date of Visit**_____

Natural History of Plexiform Neurofibromas in NF1

CONFIRMATION FAX

To:		**From:**	Brian Giglio
Site:		**WorldCare Fax::**	(617) 374-9991
Site Fax:		**WorldCare Phone:**	(617) 250-5174
Site Phone:		**Re:**	NF1 Fax Confirmation to Site

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply**

This form must be completed by WorldCare and faxed both to Boston Children's Hospital and to the appropriate patient collection center.

Date WorldCare received NF1 Data Collection Form: _____/_____/_____

Date MRI images received: _____/_____/_____

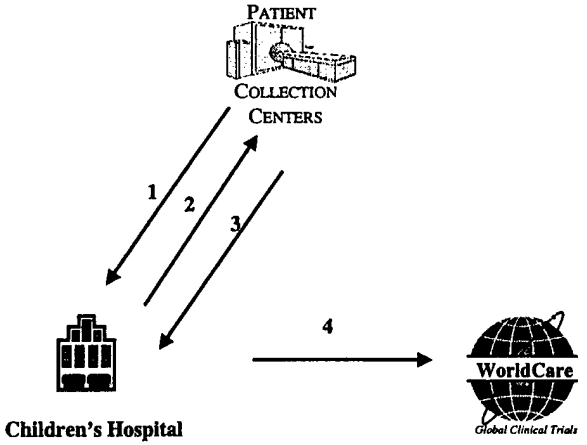
Materials completed (Y/N): _____

Material acceptable (Y/N): _____

Additional Comments: _____
_____
_____
_____

Appendix O

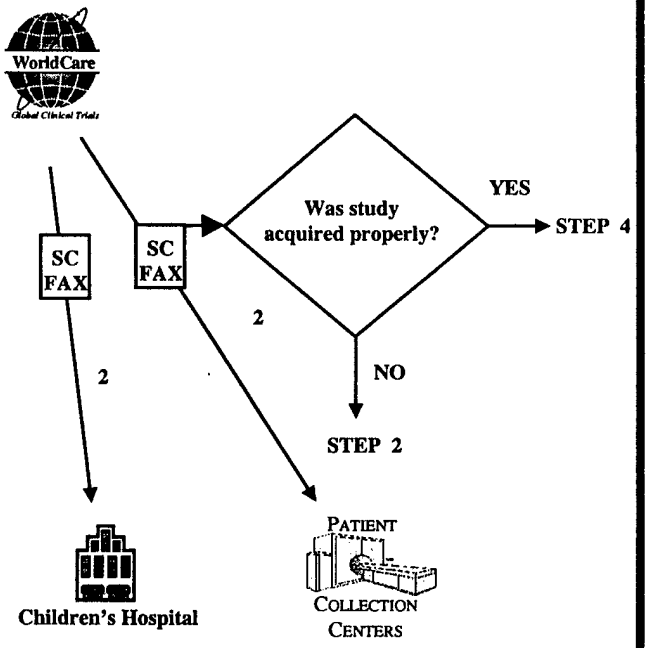
FILE TRANSFER PROTOCOL PROCEDURE



STEP 1

NOTIFICATION OF POTENTIAL PATIENT AND PATIENT ID ASSIGNMENT

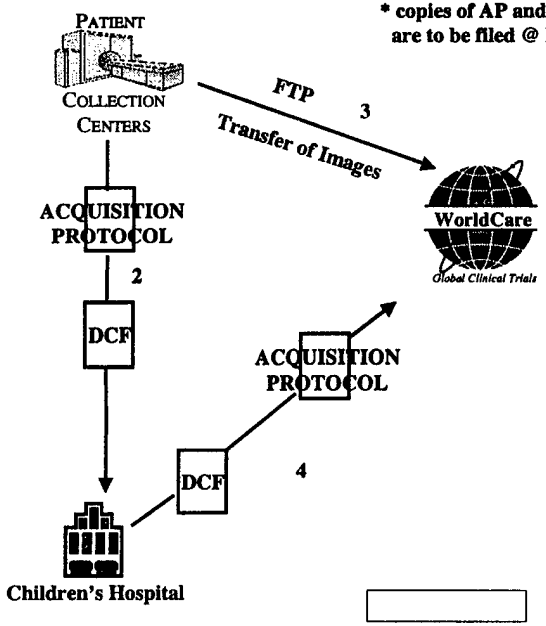
1. PCC will provide BCH with eligibility forms of potential patient.
2. If eligibility approved, BCH will assign patient ID Number and notify the PCC.
3. Via email PCC Clinical Coordinator will provide the date patient scan will be performed to BCH.
4. BCH will notify WC by fax of new patient, ID no., and the date of scan.



STEP 3

DATA QA /QC AND CONFIRMATION

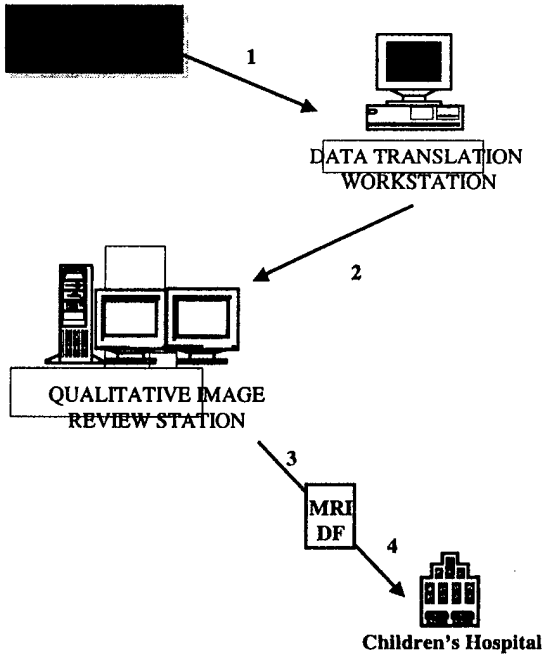
1. WC will review incoming data set for compliance with NF1 Acquisition Protocol.
2. WC will fax study confirmation fax to both PCC and BCH.
3. If data set accepted WC will proceed to next step.
4. If study deemed unacceptable WC in conjunction with BCH will request re-scan and STEP 2 will be repeated.



STEP 2

DATA COLLECTION AND DATA TRANSFER

1. PCC will scan patient per normal clinical scan and perform additional scans per the NF1acquisition protocol.
2. PCC technician will complete Acquisition Protocol form, and DCF. Fax completed originals containing to BCH.
3. Transfer patient images to WC using the appropriate FTP procedures.
4. Upon receipt of the faxed AP and DCF forms, BCH will forward these forms to WC within one business day of receipt.



STEP 4

DATA ANALYSIS AND ARCHIVAL @ WC

1. Through FTP, WC will receive data to a data translation station and and convert all data to a standard format.
2. Standardized data will be imported to a qualitative image review station.
3. WC technician will perform 3D Volumetric analysis. After radiologist review, WC will record these results on the MRI DF.
4. The original MRI DF will be forwarded to BCH and WC will maintain a copy of all data on file.

Appendix P

Billing Period: 4/1/99-6/30/99 **Invoice Date: 7/1/99**
Period: 1

Patient Visit Reimbursement Form

Natural History of Plexiform Neurofibromas in NF1

Please Note:

- As stated in the protocol, patients should be seen approximately every 6 months.
- Reimbursement is NOT contingent upon MRI scans.

Date of Visit	*Patient ID#
Total Patient Contacts:	

*Please use patient ID# assigned by Children's Hospital on the patient registration form

PAYABLE TO:

Washington University

MAILING ADDRESS:

Mary Corcoran, Assistant Controller
Washington University
7425 Forsyth
Clayton, MO 63105-2103

Return this form to: **Angela Doran**
Research Finance
Children's Hospital
Longwood Avenue
Boston, MA 02115

Attachment B

HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND (USAMRMC)

Facsimile Transmittal Header Sheet

FAX #: DSN 343-7803, (301) 619-7
Number of pages **including** this page =

From: USAMRMC, DCSRCQ
504 Scott Street
Fort Detrick, MD 21702-5012

Office Symbol: MCMR-RCQ-HR
Office of the Deputy Chief of Staff for Regulatory Compliance and Quality

Phone #: DSN 343-7486
(301) 619-7486

Internet : Sonya.Lewis@det.amedd.army.mil

Point of Contact: Sonya Lewis

To: Ms. Mary Sanford

Date: 30 September 1999

Dear Ms. Sanford:

I am sending you a list containing the various sites that have received conditional approval and final approval from the United States Army. Please note that this list comprises ten sites. Approval for Australia's consent form is pending. Considering that their Ethics Committee did not approve of the collection of blood for this study, the protocol must be amended to reflect this. Please speak with Dr. Korf regarding this issue. If additional institutions are to be included in this study, please supply me with their respective consent forms.

Sincerely,

Sonya Lewis

Sonya Lewis, MS
Human Subjects Protection Specialist

A-8394	Dr. Korf: MULTIPLE SITE NF1 STUDY Mary Sanford (coordinator)	Conditional approval letters sent out to: University of Utah **07/27/99** Children's Memorial Hospital, Chicago **07/08/99** Baylor College of Medicine, Texas **07/16/99** University of British Columbia **08/31/99** Children's Hospital Med. Ctr., Cincinnati **09/16/99** Washington University Medical Center **07/16/99** Final approval letters sent out to: Children's Hospital, Boston **06/14/99** Children's National Medical Center, Wash. DC **06/14/99** Children's Hospital Oklahoma **09/21/99** Guy's Hospital, London **09/22/99**

Attachment C

Neurofibroma Tumor Repository Progress Report

David H. Gutmann, MD-PhD
Mark Watson, MD-PhD

The Neurofibroma Tumor Repository (NTR) provides a valuable resource for ongoing as well as future studies aimed at investigating the molecular pathogenesis of NF1 plexiform neurofibromas. Over the past 12 months, we have developed the NTR infrastructure for the collection of tumor specimens as well as white blood cells. Instead of extracting DNA, RNA and protein from the blood samples received from each patient, we have instead opted to freeze white blood cells in cryopreservative. This will allow us to immortalize these leukocytes in the future when it might be necessary to procure DNA, RNA and protein. We chose this approach, as it will provide a renewable source of material. In addition, we can obtain 300 specimens from all patients enrolled in this study for future genotype-phenotype correlations. To date (9-10-99), we have received 10 blood specimens from participating clinical centers. No plexiform neurofibroma specimens have been received thus far.

Since active enrollment only commenced in June 1999, we are anticipating a large volume of specimens over the next 12 months. No problems with tissue handling have occurred and the infrastructure appears sound and highly functional.

Attachment D

Washington
WASHINGTON·UNIVERSITY·IN·ST·LOUIS
School of Medicine
Department of Pathology

Division of Neuropathology
Director
Robert E. Schmidt, M.D., Ph.D.
Richard M. Torack, M.D.
Kevin A. Roth, M.D., Ph.D.
Arie Perry, M.D.
John C. Morris, M.D.
Alan Pestronk, M.D.

October 21, 1999

Bruce R. Korf, M.D., Ph.D.
Partners Center for Human Genetics
Harvard Institutes of Medicine Building
77 Avenue Louis Pasteur, Suite 642
Boston, MA 02115

Dear Dr. Korf:

I'm writing you to officially confirm my willingness to serve as the head of the pathology core for your grant entitled "Natural History of Plexiform Neurofibromas in NF1". As such, I will make our clinical and research facilities available for the diagnostic and investigative work-up of tissue specimens obtained from patients in your study. I look forward to working with you and other members of your team. I am confident that our collaboration will be productive. Thank you for the opportunity to participate.

Sincerely,

Arie Perry

Arie Perry, M.D.
Assistant Professor of Pathology
Division of Neuropathology

AP:als

Washington University School of Medicine
at Washington University Medical Center
Campus Box 8118, 660 South Euclid Avenue
St. Louis, Missouri 63110-1093
(314) 362-7426 FAX: (314) 362-4096

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Perry, Arie	Assistant Professor of Pathology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
The University of Texas at Austin, TX	B.S.	1986	Zoology
The U. of Texas Southwestern Med. School, Dallas, TX	M.D.	1990	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE:Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publication in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

PROFESSIONAL EXPERIENCE:

1988	Autopsy Externship, Department of Pathology, Univ. of Texas Southwestern Medical School
1990-1994	Pathology Residency (AP/CP), Parkland Memorial Hospital, Univ. of Texas Southwestern Medical School
1994-1995	Surgical Pathology Fellowship, Mayo Clinic; Rochester, MN
1995-1998	Neuropathology and Research Fellowships, Mayo Clinic; Rochester, MN
1998-Present	Assistant Professor, Department of Pathology; Washington Univ. School of Medicine; St. Louis, MO

HONORS:

1993	First place resident poster presentation award, Texas Society of Pathologists
1994	First place resident podium presentation award, Texas Society of Pathologists
1994	Matthew T. Moore travel fellowship award, International Congress of Neuropathology
1995	Mary Tom Award, Canadian Association of Neuropathologists
1995-1997	American Brain Tumor Association Fellowship Award
1999	Distinguished Service Teaching Award, Washington University School of Medicine, Medical School Class of 2001

PUBLICATIONS:

Perry A, Hernandez JA: Double heterozygous hemoglobin E/Beta thalassema. ASCP Check Path. Case QAH 92-4, 1992; J162.

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Stafford SL, Perry A, Leavitt JA, Garrity JA, Suman V, Scheithauer BW, Meyer FB: Anterior visual pathway meningiomas primarily resected between 1978-88. The Mayo Clinic experience. J. Clin. Neuro-Opthalmol. 1998; 18:206-210.

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Smith JS, Tachibana I, Lee HK, Qian J, Pohl U, Mohrenweiser HW, Borell TJ, Hosek SM, Soderberg CL, von Deimling A, Perry A, Scheithauer BW, Louis DN, Jenkins RB. Mapping of the chromosome 19 q-arm glioma tumor suppressor gene using fluorescence in situ hybridization (FISH). *Oncogene*

ABSTRACTS:

Bruch LA, Hill DA, Dehner LP, Perry A: A role for FISH detection of chromosome 22q dosage in distinguishing atypical teratoid/rhabdoid tumors from central PNET/medulloblastomas. Neuro-Oncology 301; 1999.

Attachment E

The Study of Natural History of Plexiform Neurofibromas in NF1

This is a research study of the rate of growth of plexiform neurofibromas. Plexiform neurofibromas are a particular type of benign tumor that occurs in persons with neurofibromatosis type 1. The growth patterns of these tumors appear to be unpredictable and the factors that influence that growth are largely unknown. The goal of this study is to closely monitor the growth of plexiform neurofibromas for a period of at least three years using magnetic resonance imaging (MRI). This technique will permit us to measure the overall size (volume) of the plexiform neurofibroma. By repeating the assessment every 6-24 months we hope to be able to document the rate of change in size of the plexiform neurofibroma.

This is an international study in which 300 individuals with NF1 will be enrolled. The study is being directed by Bruce R. Korf, M.D., Ph.D., Clinical Director of Genetics at Boston's Children's Hospital. Patients are being recruited at 18 different institutions worldwide (see list of center locations).

This study is sponsored by the US Army Medical Research Material Command (USAMRMC). To learn more about the USAMRMC go to: http://mrmc-www.army.mil/

Participation Objectives Entry/ Exclusion Criteria Center Locations Contact Us Links

Participation

What does participation in the study mean?

Participation in this study will involve both clinical assessment and MRI scanning. The clinical assessment will occur every six months for three years. A standard physical examination will be done, the same as for a standard clinic visit. If the plexiform neurofibroma is visible on the surface it will be measured with a ruler or tape measure and photographs will be taken. Since these visits are deemed part of your clinical care, they will be billed to your medical insurance as standard clinical visits. A clinic note will be placed in the medical record and copies sent to your primary care provider, as is standard in the clinic. Data about your clinical assessment will be entered into a computer database. This clinical data is also sent to a central database maintained by the University of British Columbia, sponsored by the National Neurofibromatosis Foundation. You will be identified in this central database only by a code number, but not by name, to preserve confidentiality. Photographs of your plexiform neurofibroma will be kept in a confidential file in the Division of Genetics. Clinic visits will occur over a period of 30-45 minutes.

At the time of the first clinic visit when this study begins a blood sample will be obtained from you. The blood sample will be drawn from a vein in the arm, and will consist of approximately 5 – 10 cc (1 – 2 teaspoons). This sample will be used as a source of DNA, the genetic material inside our cells. We will also obtain serum (the liquid component of blood). This DNA and serum will be sent to a central tissue repository at Washington University in St. Louis and banked there. There are no immediate plans to study this DNA and serum, but at some point in the future it may be possible to examine the DNA for the changes in the NF1 gene, or in other genes that may alter the behavior of neurofibromas. The serum may be used to test for substances in the blood that cause neurofibromas to grow. Since we will be monitoring the growth of the neurofibroma carefully, we hope to have the opportunity to examine genetic or serum factors that may influence tumor growth at some point in the future. There is no assurance, however, that such testing will be possible or necessarily will be done. Any results obtained from DNA or serum studies will be kept confidential. You will have the opportunity to designate whether you would like to learn the results of such testing in the future, and whether you would like us to share these results with any health providers whom you designate. You can direct us to withdraw the blood sample from the repository at any time.

MRI scanning of the plexiform neurofibroma will be part of this study. Every participant will have an MRI at the time of enrollment into the study (unless the plexiform neurofibroma has been followed by MRI for a period of time before the study and is known to have not changed in size). A second MRI will be done one year later unless there are clinical reasons to do it sooner. MRI will be repeated at the end of the study, at three years. If the neurofibroma appears to be growing, either based on clinical assessment or from measurements of the MRI scans, follow-up MRI may be done more often, at the discretion of your physician, in accordance with standard clinical care.

In most cases these MRI scans are used in standard clinical care and will therefore be billed to your insurance. There may be some instances in which an MRI might not have been performed for routine clinical purposes at the same time as designated by the study. In these cases, funds are available to defray the costs of the MRI scan. In some instances it will be necessary to use sedation or general anesthesia. Consent for this procedure will be obtained by the radiologist or anesthesiologist prior to the procedure. Also, in some cases, it will be necessary to insert an intravenous line and administer contrast material into the vein. This will be done at the discretion of the radiologist, if it appears that contrast is necessary to better visualize the neurofibroma. Your consent will be obtained prior to this procedure. We expect that the MRI scans will require approximately one hour.

We do not plan to perform surgery or take a sample of the plexiform neurofibroma as part of this study, but in some cases surgery may be performed because of clinical indications. This decision will not be influenced by your participation in the study, and will not affect your participation in the study. If there is neurofibroma tissue available that is not needed for examination as part of clinical care, this tissue will be collected and sent to a central tissue bank at Washington University in St. Louis. In addition, a sample will be sent to Mt. Sinai School of Medicine for review of the pathological features of the neurofibroma. The tissue will be identified with a code number, and will only be possible to connect with your name through our clinic. The tissue may be distributed to investigators to help with their research on neurofibromatosis. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. It is not anticipated that results of study of your neurofibroma tissue will influence clinical management, and therefore you will not be informed of research results on this tissue. All research results will be kept confidential. You can withdraw your specimen from the tissue repository at any time.

Study Objectives

A. Determine the efficacy of volumetric MRI for measurement of the growth rate of plexiform neurofibromas.

B. Provide a body of normative data on the growth rate of plexiform neurofibromas. Although limited by a relatively short study period, the following hypotheses will be tested:

- **Most plexiform neurofibromas grow out of proportion with somatic growth fo period of time during childhood but reach a plateau by the end of puberty;**
- **Patterns of neurofibroma growth may vary from patient to patient but there ar systematic differences in growth patterns according to location of the neurofibroma in the body;**

C. Establish a consortium of clinical centers supported by a tissue repository and central review of pathology, radiology, and statistical data.

Entry Criteria

A. **Diagnosis of Neurofibromatosis:** All study subjects will fulfill diagnostic criteria for NF1.

B. **Plexiform Neurofibroma:** A plexiform neurofibroma fulfilling entry criteria for the study will be defined as a diffuse soft tissue or nerve enlargement in a patient with NF1 that is causing or has potential to cause disfigurement or functional disability.

C. **Distribution of Plexiform Neurofibromas by site:** A total of 300 plexiform neurofibromas will be studied, consisting of 100 tumors in the following three groups (based on region of maximal involvement):

   1. **Head and Neck**
   2. **Trunk and Limbs (externally visible)**
   3. **Trunk and Limbs (internal)**

Exclusion Criteria

A. Presence of metallic implant that will make the patient unable to have MRI studies

B. Presence of medical or psychological condition that will make the patient unable to tolerate MRI studies or anesthesia (if needed)

C. Inability to image tumor or define tumor margins by MRI (which may be determined after the initial study)

D. Failure to obtain initial MRI within 60 days of enrollment

E. Previous radiation therapy to site of plexiform neurofibroma

F. Surgery involving the plexiform neurofibroma (excluding biopsy) within a six month period before enrollment

G. Current antineoplastic therapy

Center Locations and Physicians

Alan Rubenstein, M.D.
Mt. Sinai School of Medicine
1 Gustave Levy Place
New York, NY 10029

Bruce R. Korf, M.D., Ph.D.
Children's Hospital
300 Longwood Ave.
Boston, MA 02115

David Gutmann, M.D., Ph.D.
Washington University School of Medicine
660 S. Euclid Ave.
St. Louis, MO 63110

David Viskochil, M.D., Ph.D.
University of Utah, School of Medicine
Division of Medical Genetics
413 MREB 50 N. Medical Dr.
Salt Lake City, UT 84112

Eric Legius, M.D.
University of Leuven
Kon Elisabethlaan 20
Leuven B-3000 Belgium

Fernando Kok, M.D.
University of Sao Paulo
de Grendo Juliete 233
04721060
Sao Paulo, Brazil

Jan Friedman, M.D., Ph.D.
University of British Columbia
4500 Oak St.
Vancouver, BC

Joel Charrow, M.D., Ph.D.
Children's Memorial Hospital
2300 Children's Plaza
Chicago, IL 60614

John J. Mulvihill, M.D.
Children's Hospital of Oklahoma
940 NE 13th St., Room 2418
Oklahoma City, OK 73104

Kathryn North, M.D.
Royal Alexandra Hospital
PO Box 3515
Parramatta, NSW 2124
Australia

Mia MacCollin, M.D., Ph.D.
Massachusetts General Hospital
Bldg 149, 13th St., Boston, MA 02129

Robert Hopkins, M.D.
Children's Hospital Medical Center
3333 Burnet Ave., Cincinnati, OH
45229-2899

Roger Packer, M.D.
Children's National Medical Center
111 Michigan Ave. NW
Washington, D.C. 20010

Rosalie Ferner, M.D.
Guys Hospital
St. Thomas' St.
London, UK
SE1 9RT

Sharon Plon, M.D., Ph.D.
Texas Children's Hospital
Division of Hematology-Oncology
6621 Fannin St., 3-3320
Houston, TX 77030

Susan Huson, M.D.
Oxford University
Department of Clinical Genetics
Churchill Hospital
Headington, Oxford, UK
0X3 7LJ

Victor-Felix Mautner, M.D.
Klinikum Nord Ochsenzoll
Langenhorner Chaussee 560

22419 Hamburg, Germany

Study Home Page Participation Objectives Entry/ Exclusion Criteria Contact Us Links

If you or your child would like to participate in the Study of Natural History of Plexiform Neurofibromas in NF1 or you would like

If you or your child would like to participate in the Study of Natural History of Plexiform Neurofibromas in NF1 or you would like further information please contact:

Mary Sanford
Research Study Coordinator
Children's Hospital
Division of Genetics
300 Longwood Avenue
Boston, MA 02115
Phone: (617) 355-3479
Fax: (617) 355-7588
Email: sanford_m@hub.tch.harvard.edu

CONTACT US: sanford_m@hub.tch.harvard.edu

Neurofibromatosis Links

Link to the National Neurofibromatosis Foundation (NNFF)
http://www.nf.org/

Link to the NIH National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/HEALINFO/DISORDER/NEUROFIB/NEUROFIB.HTM

Link to the Massachusetts General Hospital NF Clinic home page
http://neurosurgery.mgh.harvard.edu/NFclinic.htm

Link to the Neurofibromatosis Resources Webpage
http://neurosurgery.mgh.harvard.edu/NFR/

Link to the University of Washington at Seattle Gene Clinic
http://www.geneclinics.org/profiles/nf1/

Link to NF Inc.
http://www.nfinc.org/

Link to The Neurofibromatosis Web. A place for people with NF to communicate with each other.
http://193.192.226.150:80/neurofibromatosis/

Link to the NF Inc. Links Page
http://www.nfinc.org/links.html

If you would like to add a website to this list, please contact Mary Sanford at:
sanford_m@hub.tch.harvard.edu

Attachment F

WorldCare
Global Clinical Trials

To: Mary Sanford

From: Brian Giglio

CC: Bruce Korf, Jay Zimmerman, Colette Lajeunesse

Date: 10/28/99

Re: Army Report for Natural History of Plexiform Neurofibromas in NF1

---

a) List of all centers that have submitted test data

The following MRI centers have submitted test data for the NF1 Study either by optical disk or through File Transfer Protocol (FTP):

1. Children's Hospital
Neurofibromatosis Program
300 Longwood Ave.
Boston, MA 02115

2. Center for Human Genetics
University of Leuven
Kon Eliaabethlaan 20
Leuven B-3000, Belgium

3. Children's Hospital Medical Center
Neurofibromatosis Center
3333 Burnet Ave.
Cincinnati, OH 452229 - 2899

4. Children's Memorial Hospital
Neurofibromatosis Clinic
2300 Children's Plaza
Chicago, IL 60614

5. Children's Hospital of Oklahoma (CHO)
Neurofibromatosis Program
940 NE 13th St. Room 2418
Oklahoma City, OK 73104

6. Children's National Medical Center
Neurofibromatosis Program
111 Michigan Ave.
Washington, D.C. 20010

7. Guys Hospital
Neurofibromatosis Program
St. Thomas' St.
London, UK SE1 9RT

8. Klinikum Nord Ochsenzol
Neurological Department
Langenhomer Chausee 560
D-22419 Hamburg, Germany

9. Massachusetts General Hospital
Neurofibromatosis Clinic
Building 149
13th Street
Charlestown, MA 02129

10. Mount Sinai Medical Center
Department of Neurology
One Gustave L. Levy Place
New York City, NY 10029-6574

11. Royal Alexandria Hospital
Neurofibromatosis Clinic
PO Box 3515
Parramatta, NSW
2124, Australia

12. Texas Children's Hospital
Division Hematology - Oncology
6621 Fannin St., 3 - 3320
Houston, TX 77030

13. University of British Columbia
Room C201
4500 Oak St.
Vancouver, British Columbia V6T1Z3

14. University of Utah
Division of Medical Genetics
413 MREB
50 N. Medical Dr.
Salt Lake City, UT 84112

15. Washington University
Neurofibromatosis Program
St. Louis Children's Hospital
Box 8111
660S. Euclid Ave.
St. Louis, MO 63110

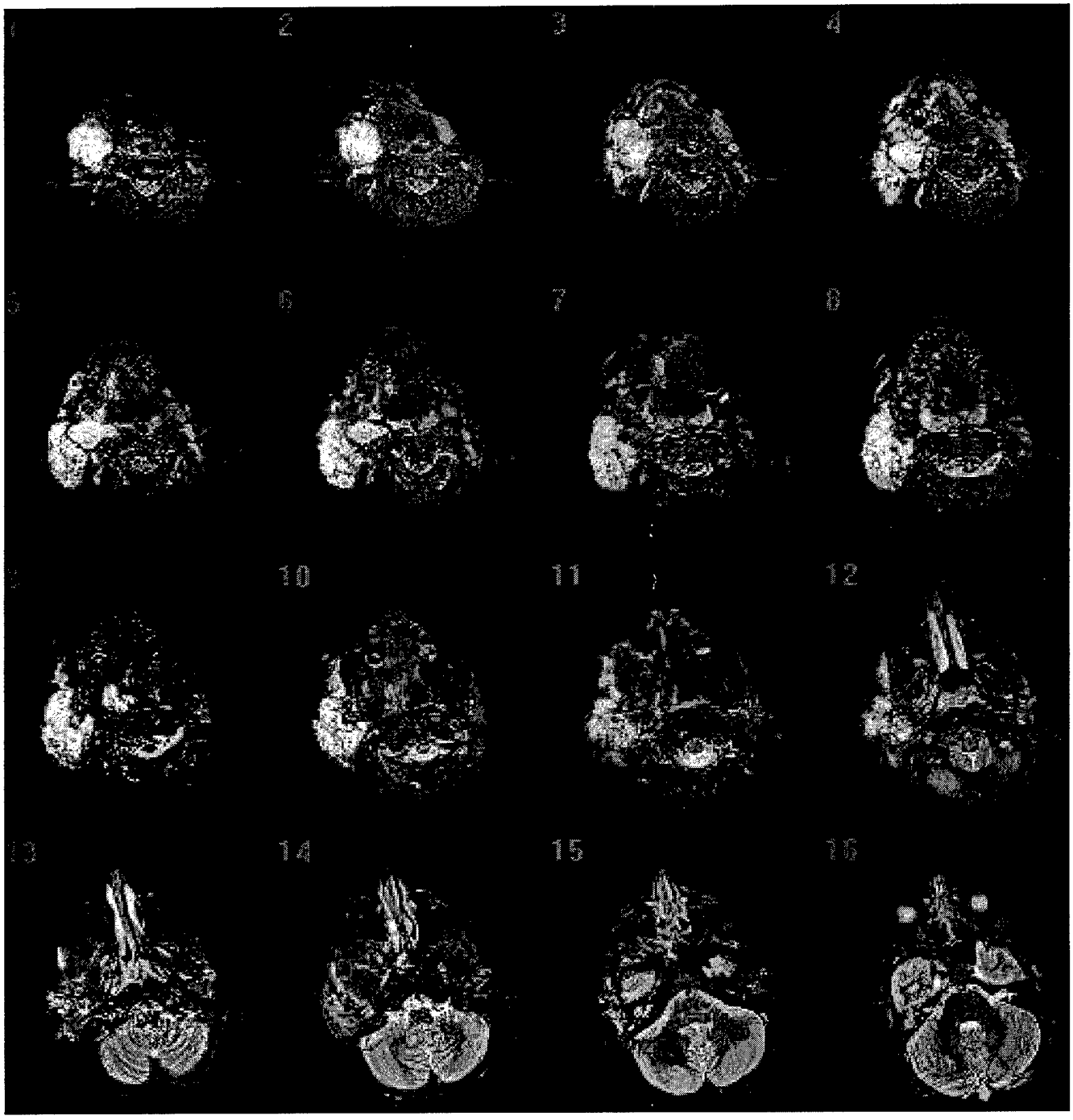
Only one of these MRI centers, Guy's Hospital, has submitted a test data set that is not compatible with WorldCare's image viewing and measurement software. This issue is related to file corruption and another test data transfer is currently being addressed.

b) List of patient visits from each center
A total of twelve patient visits have been sent to WorldCare from two MRI centers to date. The following is a list of the patient visits received from each center:

Children's Hospital, Boston	Children's Hospital, Oklahoma
1. 107-0123-500	1. 178-0002-001
2. 107-0316-500	2. 178-0001-001

3. 107-0200-500	
4. 107-0632-500	
5. 100-0145-500	
6. 107-0160-500	
7. 107-0021-500	
8. 107-0055-402	
9. 107-0520-500	
10. 107-0524-500	

c) Example of volumetric data
The following is the image and measurement data resulting from volumetric analysis performed by a WorldCare technician on an NF1 sample patient:



The following spreadsheet tabulates the measurement results for each region of interest (ROI) in order to calculate the volume on the images displayed above for the NF1 sample patient:

NF1 Sample Patient

Document	Mean	Max	Min	Std. Dev.	Area	Sum	Volume
f.des[1,1](RED)	807.97864	1383	73	269.03	1229.41	1,476,177.00	7376.476
f.des[2,1](RED)	766.94104	1338	83	279.91	1460.89	1,665,029.00	8765.369
f.des[3,1](RED)	743.37592	1379	119	221.15	1537.61	1,698,614.00	9225.642
f.des[3,1](RED)	737.92499	1054	309	177.13	53.8331	59,034.00	322.9984
f.des[3,1](RED)	594.90625	970	171	185.65	43.0665	38,074.00	258.3987
f.des[4,1](RED)	655.15625	1344	16	246.76	2652.62	2,582,626.00	15915.75
f.des[5,1](RED)	717.37024	1325	132	232.24	3004.56	3,203,058.00	18027.35
f.des[6,1](RED)	813.12482	1407	74	223.69	2194.37	2,651,600.00	13166.22
f.des[7,1](RED)	907.1087	1608	184	242.60	1634.51	2,203,367.00	9807.04
f.des[8,1](RED)	844.96515	1408	179	246.10	1873.39	2,352,383.00	11240.35
f.des[9,1](RED)	839.02924	1466	134	259.88	1979.71	2,468,424.00	11878.27
f.des[10,1](RED)	857.86762	1459	163	247.93	1849.84	2,358,278.00	11099.03
f.des[11,1](RED)	802.18988	1525	141	256.24	1701.13	2,027,936.00	10206.75
f.des[12,1](RED)	673.17322	1528	93	274.76	1526.84	1,527,430.00	9161.043
f.des[13,1](RED)	436.95856	1222	19	190.20	1866.66	1,212,123.00	11199.97
f.des[14,1](RED)	413.65042	1238	0	191.52	1476.37	907,549.00	8858.232
f.des[15,1](RED)	450.0625	1348	40	177.97	538.331	360,050.00	3229.984
						Volume=	159.74 CM^3

d) Description of WorldCare's efforts in establishing the infrastructure and data analysis

WorldCare has contributed to the NF1 Natural History Study infrastructure by preparing the WorldCare site for data collection and analysis and preparing the MRI centers for data collection and transfer. A private suite for the NF1 Natural History Study was prepared at WorldCare, Inc and houses hardware and software for sending and receiving images for the collection and analysis of patient data, including optical drives and translators. Also, a filing system, logbooks, and patient tracking database have been established to accept and track the workflow of patient data.

Standard operating procedure manuals were completed for both the WorldCare measurement center and the MRI centers. These manuals outline procedures for the collection, receiving and analysis of data specific to the study within Good Clinical Practices (GCP) guidelines. The MRI center SOP was merged with the NF1 Study Manual and has been distributed to the clinical coordinators at each MRI facility in the study. The WorldCare Measurement Center SOP has been entered into WorldCare Document Control and will be revised on as needed basis.

To date, WorldCare has qualified fifteen MRI facilities for the study. Each facility was required to complete a site survey detailing both MRI scanner and network hardware and software specifications. If these specifications fulfilled study guidelines, WorldCare requested a test data set to be sent either via FTP or on optical disk. A review of this test data ensured that the facilities' images and their method of data transfer were compatible with WorldCare's image viewing and analysis systems.

Both qualitative and quantitative analyses have been performed on ten enrolled patients. These patients were scanned and collected within the study protocol parameters. The images were collected and measured by a WorldCare Measurement Center Technician providing volumetric measurements of the plexiform neurofibromas. A sub-specialist radiologist will review these

measurements, and the finalized measurement results of the volumetric analysis will be recorded and forwarded to the NF1 Research Coordinator.

A radiologist review meeting is scheduled for November 1, 1999. Children's Hospital NF1 radiologists will review the first data sets measured by WorldCare technicians. This meeting will also be used to establish parameters for a validation study. This study will require WorldCare technicians and NF1 radiologists to perform volumetric analysis on the same patients. A Children's Hospital statistician will analyze these results to determine the variability between readers for volumetric analysis of NF1 plexiform neurofibromas. This study will be completed by January 1, 2000 providing the first publication of the NF1 study.

Attachment G

P.O#:

Ship To:
WorldCare

CLINICAL TRIAL DIVISION

WORLDCARE, INC.
One Cambridge Center
Cambridge, MA 02142
Phone: (617) 374-9001
Fax: (617) 374-9991

Invoice

Bill To:
Dr. Bruce Korf
Children's Hospital
300 Longwood Ave.

Boston, MA 02115

Invoice Number 1722

Date Shipped:

Invoice Date: 11/17/98

Item Description	Serial #	Price
Import Workstation with high resolution monitor		$2,625.00
Dual Headed Analysis and Review Workstation		$4,750.00
Pioneer Optical Drive		$1,350.00
Network Equipment		$200.00
2 Copies MEDStudio Pro Analysis Software		$7,500.00
1 Copy GE/SIEMENS Optical Reader		$5,000.00
4 year service contract for machines at WC		$4,000.00

Shipping & Handling: NA

Terms: Net 30 Days **Total:** $25,425.00

Make checks payable to: WorldCare, Inc.

NF1 / NF2 Equipment

Import Workstation

450 MHz Pentium II Processor
128 Meg. SDRAM
Keyboard, Intellimouse
40X CDROM
16 MB STB mVidia AGP Video Card
1.44 MB Floppy

16.8 Gig Hard Drive
McAfee Virus Scan
Microsoft Windows 98
3COM 3C905B 10/100 PCI NIC
21" Hitachi Superscan 814 Monitor

Dual Headed Analysis and Review Workstation

450 MHz Pentium II Processor
256 Meg. SDRAM
Keyboard, Intellimouse
40X CDROM
Appian JeronimoPro 16 MB Video Card
1.44 MB Floppy

16.8 Gig Hard Drive
McAfee Virus Scan
Microsoft Window NT
3COM 3C905B 10/100 PCI NIC
(2) 21" Hitachi Superscan 814 Monitors
HPLaserjet Printer

Pioneer Optical Drive

Pioneer Optical Drive for reading Pioneer 502 and 702 opticals from scanners

Network Equipment

10/100 5 port HUB with uplink and Cat 5 cables

MEDStudio Pro Analysis Software

Software to perform the data review and analysis for 2D and 3D measurements

GE/SIEMENS Optical Reader

Software to retrieve and convert images stored on the proprietary GE and SIEMENS formatted optical disks (Pioneer 502/702) to DICOM 3.0 files.

3 or 4-year service contract for machines at WC

Full support for all hardware and software used in this trial including regular preventative maintenance.

Attachment H

Group A
Head and Neck - Child

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
A01	170-0001-001	Packer	CNMC	6/17/99	8/23/99	8/23/99					
A02	107-0200-500	Korf	CH	7/23/99				7/27/99			
A03	107-0524-500	Korf	CH	8/11/99							
A04	107-0521-500	Korf	CH	8/11/99							
A05	107-0033-500	Korf	CH	8/11/99							
A06	107-0032-500	Korf	CH	8/11/99							
A07	107-0050-500	Korf	CH	8/23/99							
A08	178-0001-001	Mulvihill	CHO	10/21/99							
A09											
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Group A
Head and Neck - Child

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
A31											
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Group B
Head and Neck - Adult

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
B01	107-0261-500	Korf	CH	8/31/99				10/1/99			
B02	168-007-0001	Ferner	GH	10/21/99							
B03	168-008-0001	Ferner	GH	10/21/99							
B04	168-005-0001	Ferner	GH	10/21/99							
B05	168-017-0001	Ferner	GH	10/21/99							
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Group B
Head and Neck - Adult

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
B31											
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Group C
Trunk and Limbs (Externally Visible) - Child

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
C01	170-0000-000	Packer	CNMC	10/21/99							
C02	107-0520-500	Korf	CH	7/22/99				7/16/99			
C03	170-0006-006	Packer	CNMC	8/2/99	8/23/99	8/23/99					
C04	107-0160-500	Korf	CH	8/11/99				8/25/99			
C05	107-0491-500	Korf	CH	8/11/99							
C06	107-0632-500	Korf	CH	8/11/99							
C07	107-0618-500	Korf	CH	8/11/99							
C08	107-0021-500	Korf	CH	8/11/99							
C09	107-0017-500	Korf	CH	8/23/99							
C10	107-0123-500	Korf	CH	8/23/99				8/19/99			
C11	168-003-0001	Ferner	GH	10/21/99							
C12	168-018-0001	Ferner	GH	10/21/99							
C13	178-0003-002	Mulvihill	CHO	10/21/99							
C14	178-0004-001	Mulvihill	CHO	10/21/99							
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Group C
Trunk and Limbs (Externally Visible) - Child

				Visit #1							
Study ID#	Database ID#	Physician	Institution	Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
C31											
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Group D
Trunk and Limbs (Externally Visible) - Adult

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
D01	170-0002-002	Packer	CNMC	6/18/99	8/23/99	8/23/99					
D02	170-0004-004	Packer	CNMC	6/24/99	8/23/99	8/23/99					
D03	107-0316-500	Korf	CH	8/10/99				8/9/99			
D04	107-0020-503	Korf	CH	8/23/99							
D05	107-0130-500	Korf	CH	9/8/99	10/21/99	10/21/99					
D06	168-0006-001	Ferner	GH	10/21/99							
D07	168-0004-001	Ferner	GH	10/21/99							
D08	168-0009-001	Ferner	GH	10/21/99							
D09	168-0010-001	Ferner	GH	10/21/99							
D10	168-0011-001	Ferner	GH	10/21/99							
D11	168-0012-001	Ferner	GH	10/21/99							
D12	168-0002-001	Ferner	GH	10/21/99							
D13	168-0001-001	Ferner	GH	10/21/99							
D14	168-0013-001	Ferner	GH	10/21/99							
D15	168-0014-001	Ferner	GH	10/21/99							
D16	168-0015-001	Ferner	GH	10/21/99							
D17	168-0016-001	Ferner	GH	10/21/99							
D18	168-0019-001	Ferner	GH	10/21/99							
D19	168-0020-001	Ferner	GH	10/21/99							
D20	178-0003-001	Mulvihill	CHO	10/21/99							
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Group D
Trunk and Limbs (Externally Visible) - Adult

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
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Group E
Trunk and Limbs (Internal) - Child

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
E01	170-0003-003	Packer	CNMC	6/23/99	8/23/99	8/23/99					
E02	178-0002-001	Mulvihill	CHO	10/21/99							
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Group E
Trunk and Limbs (Internal) - Child

				Visit #1							
Study ID#	Database ID#	Physician	Institution	Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
E31											
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Group F
Trunk and Limbs (Internal) - Adult

Study ID#	Database ID#	Physician	Institution	Visit #1							
				Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
F01	170-0005-005	Packer	CNMC	7/20/99	8/23/99	8/23/99					
F02	107-0055-402	Korf	CH	7/23/99				1/11/99			
F03											
F04											
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Group F
Trunk and Limbs (Internal) - Adult

				Visit #1							
Study ID#	Database ID#	Physician	Institution	Date Enrolled	Core Data Forms Received	Data Forms Received	Photos Received	MRI Date	MRI Data Received	MRI Data Confirmed by WC	Billed
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Attachment I

ANNOUNCEMENT

We will be holding a meeting on the subject of Clinical Trials in Neurofibromastosis Type 1 and the ***Study of Natural History of Plexiform Neurofibromas in NF1***.

Friday July 16, 1999
12:00 - 3:00 PM

Children's Hospital
Enders Auditorium
320 Longwood Ave
Boston, MA 02115

The purpose of this meeting is to provide an update on clinical trials in NF1 and to describe the new study on the natural history of plexiform neurofibromas in NF1.

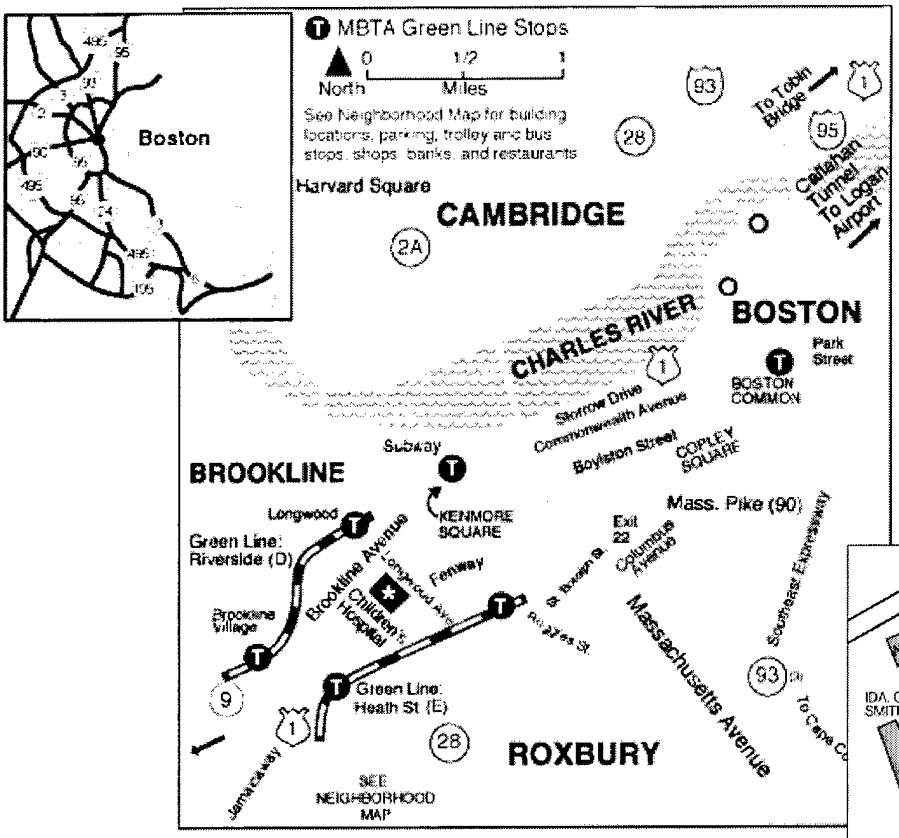
For more information please contact
Mary Sanford, Study Coordinator at (617) 355-3479 or
sanford_m@hub.tch.harvard.edu

Speakers will be **Bruce Korf, M.D., Ph.D.** and **Gretchen Schneider, M.S.**, Coordinator of the Neurofibromatosis Program.

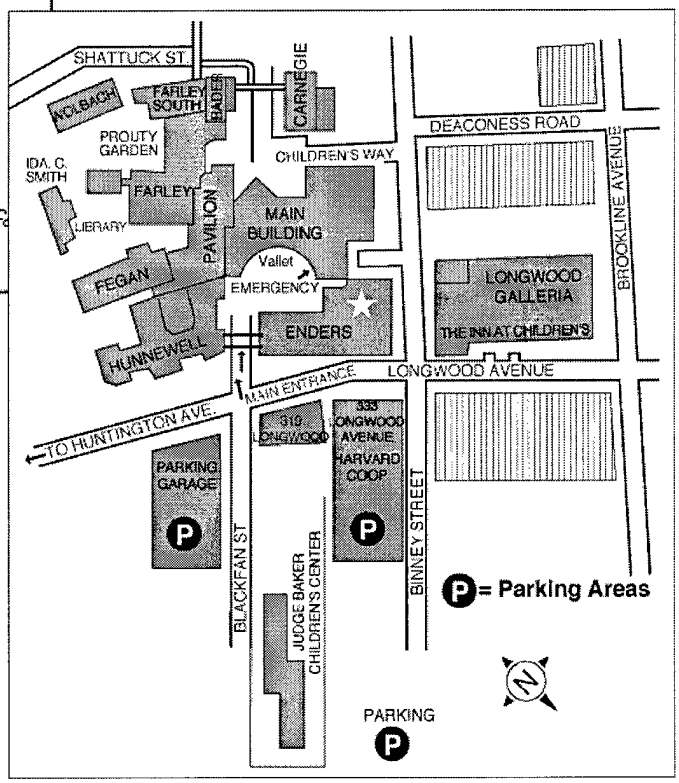
NF Clinic
Children's Hospital
Fegan 10
300 Longwood Avenue
Boston, MA 02115

Children's Hospital

RETURN SERVICE REQUESTED



Parking is available at the Children's Hospital Parking Garage on the corner of Longwood Ave and Blackfan St.



For detailed directions visit the Children's Hospital Website

www.childrenshospital.org

Attachment J

NATURAL HISTORY OF PLEXIFORM NEUROFIBROMAS IN NF-1

This meeting is funded by the U.S. Army Medical Research with additional support from the National Neurofibromatosis Foundation

The Banbury Center, Cold Spring Harbor Laboratory, 6-9 February 1999

PROGRAM

Saturday, 6 February

Afternoon	Arrival at Robertson House, Banbury Center, for registration and room assignment
6:00 pm	Reception at Robertson House
7:30 pm	Dinner at Robertson House

Sunday, 7 February

7:00-8:15 am	Breakfast at Robertson House
8:30-12:30 pm	**SESSION I:**
8:30-8:50 am	Bruce R. Korf, Children's Hospital, Boston, Massachusetts Peter Bellermann, The National Neurofibromatosis Foundation, Inc., New York, New York Jan A. Witkowski, Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York: Welcome and Introduction
8:50-9:30 am	Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Overview of Project.
9:30-9:50 am	William Slattery, House Ear Institute, Los Angeles, California: Overview of NF2 Project.
9:50-10:20 am	Break
10:20-10:50 am	Susan Huson, The Churchill Hospital, Oxford, United Kingdom: Patterns of Plexiform Neurofibromas in Different Anatomical Locations.
10:50-11:50 am	Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Subject Acquisition Protocols.

11:50-12:30 pm	Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Reimbursement and Administration.
12:45 pm	Luncheon at Robertson House
2:00-5:30 pm	**SESSION II: MRI Protocol**
2:00-2:30 pm	Diego Jaramillo, Children's Hospital, Boston, Massachusetts: MRI of Peripheral Plexiform Neurofibromas (including Protocol).
2:30-3:00 pm	Tina Young Poussaint, Children's Hospital, Boston, Massachusetts: MRI of Cranial and Spinal Plexiform Neurofibromas (including Protocol).
3:00-3:20 pm	Jay Tsuruda, University of Utah, Salt Lake City:
3:20-3:50 pm	Break
3:50-4:50 pm	Jay B. Zimmerman, WorldCare, Inc., Cambridge, Massachusetts: WorldCare MRI Protocol.
4:50-5:30 pm	James DiCanzio, Children's Hospital, Boston, Massachusetts: Statistical Analysis of Radiological Data.
6:00 pm	Reception at Robertson House
7:00 pm	Dinner at Robertson House

Monday, 8 February

7:30-8:45 am	Breakfast at Robertson House
9:00-12:30 pm	**SESSION III: Clinical and Pathological Data**
9:00-10:00 am	Jan M. Friedman, University of British Columbia, Vancouver, Canada: Clinical Database.
10:00-10:20 am	Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Patient Questionnaire.
10:20-10:50 am	Break
10:50-11:30 am	David Wolfe, Mt. Sinai Medical Center, New York, New York: Histopathologic Correlates of Growth in Plexiform Neurofibroma.

11:30-12:30 pm	David Wolfe, Mt. Sinai Medical Center, New York, New York and Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Pathology Review Facility.
12:45 pm	Luncheon at Robertson House
2:00-5:30 pm	**SESSION IV: Tissue Bank and Cell Biology**
	Studies of Cell Biology
2:00-2:30 pm	Lynn Rutkowski, Abramson Center, Philadelphia, Pennsylvania: Understanding biological defects in neurofibroma-derived Schwann cells. Part 1: Resolving obstacles.
2:30-3:00 pm	Nancy Ratner, University of Cincinnati College of Medicine, Ohio: Neurofibroma-Derived Schwann Cells are invasive and Show High Ras-GTP.
3:00-3:30 pm	David Viskochil, University of Utah, Salt Lake City: Somatic DNA Alterations in Peripheral Nerve Sheath Tumors.
3:30 pm	Break
3:30-5:30 pm	David H. Gutmann, Washington University School of Medicine, St. Louis, Missouri: Administration of Tissue Bank and Mechanisms.
6:00 pm	Reception at Robertson House
7:00 pm	Dinner at Robertson House

Tuesday, 9 February

7:30-8:45 am	Breakfast at Robertson House
9:00-12:15 pm	**SESSION V: Logistical Issues**
9:00-10:30 am	Bruce R. Korf: Children's Hospital, Boston, Massachusetts:
	Time Line Publication of Policy Finance Consent
10:30 am	Break

10:30-12:15 pm	Logistical Issues (Cont'd) Bruce R. Korf: Children's Hospital, Boston, Massachusetts
12:30 pm	Luncheon at Robertson House
	Afternoon departure

NATURAL HISTORY OF PLEXIFORM NEUROFIBROMAS IN NF-1

The Banbury Center, Cold Spring Harbor Laboratory, 6-9 February 1999

INVITED PARTICIPANTS

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